



# **Genomics and the Chemical Industry**

**Carol J. Henry, Ph.D., D.A.B.T.  
American Chemistry Council**

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and  
Data on Environmental Contaminants  
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# A Third Species of African Elephants?

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# Revolution in Biology

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- Sequencing of the human genome
- “Omics”
  - Genomics, proteomics, metabonomics, transcriptomics
  - Bioinformatics
  - Computational Toxicology
- State of the technology
- State of understanding

# The Promise of Genomics

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- Opportunity for predictive toxicology and screening;
- Identification and quantification of susceptible populations;
- Identification of biomarkers of chemical exposure and effects;
- Opportunity to explore multiple interactions between genetic, biological, and environmental stressors;
- Synthesis of disparate disciplines.

# Chemical Industry Research and Development

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- Chemical R&D plays a critical role in US economy
- In 1998, \$68 billion in exports; 10% of all exports
- Breakthrough advances in numerous fields, including agriculture, transportation, housing, electronics, communications, biochemistry, national defense, and environmental protection.

# Chemical Industry Perspective

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- Use and application of new technologies will be implemented by the chemical industry in its R&D efforts.
- Managing the potential impact of chemicals on human and environmental health requires scientifically advanced methods.
  - “Genomics” will play a major role for the society and the chemical industry

# Findings of a Workshop<sup>1</sup>

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- “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

<sup>1</sup>*Environmental Health Perspectives, 2002 Oct;110(10):1047-50*

# Technical Issues to be Resolved

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- Technical understanding and shared learning in the public domain;
- Development of publicly accessible gene expression databases;
- Establishment of predictive nature of assays before widespread application to risk assessment;
- Identifying relevant markers of gene expression in humans;
- Absence of background prevalence data in humans.

# Policy Issues to be Resolved

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- Advice should be sought for social and ethical issues;
- Premature use of “omics” data;
- Uncertainty of regulatory positions on “omics” data.

# EPA Interim Genomics Policy

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- Genomics data and analyses will significantly impact many areas of scientific research and human and ecological health assessments.
  - May allow EPA to enhance assessments and better inform the decision-making process
- EPA must understand how to develop and use the research tools made possible from genomics.
  - Understand the appropriate uses of genomics data to inform Agency decisions.

# EPA Interim Genomics Policy (cont.)

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- EPA encourages further research on methods development, methods evaluation, and data collection to address existing gaps in knowledge concerning the consequences of genomic changes.
- Parallel need to:
  - Develop information technologies,
  - Research on data analysis,
  - Applications of genomics to computational toxicology.

# Research Recommendations: Toxicology

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- “Omics” and mechanism of action and dose-response
- Link “omics” to traditional toxicology endpoints
- Relevance of “omics” response to phenotype (adaptive/adverse responses)
- “Omics” and reduction of uncertainties with animal-human extrapolation

# Research Recommendations: Epidemiology

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- Characterize prevalence and background of genetic polymorphisms and their functions
- Focus on methods to assess gene expression in large populations
- Address statistical and bioinformatics issues
- Use multidisciplinary approach to epidemiology research

# International Ecotoxicogenomics Workshop

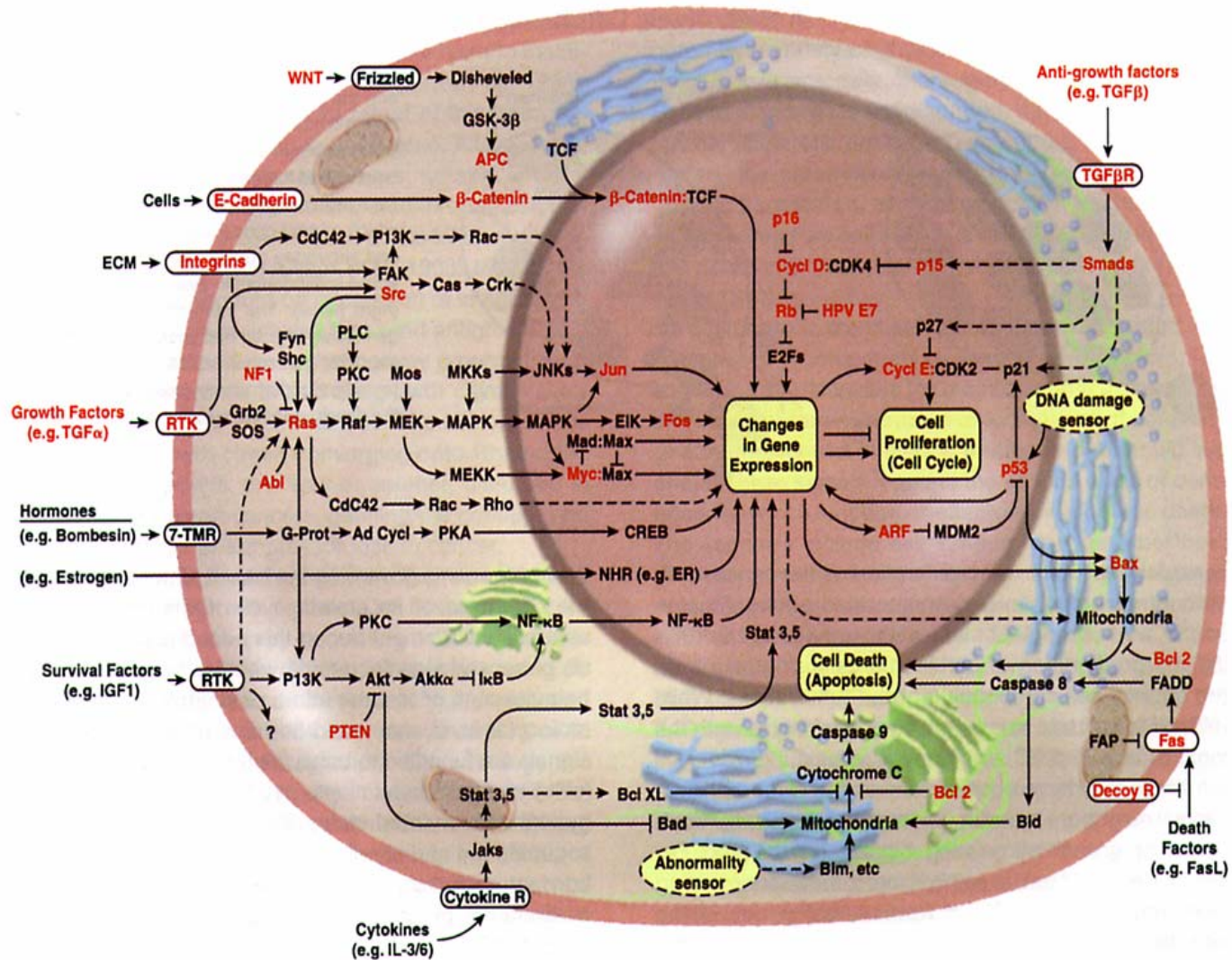
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- 23-25 September, 2002 in Pensacola, Florida
- Outcome:
  - Need for unified research agenda
  - Need to synthesize disparate disciplines
  - Need for multi-stakeholder collaboration
- Inextricable linkage between human and ecological risk assessment
  - Development of 'omics' tools
  - Application to risk assessment

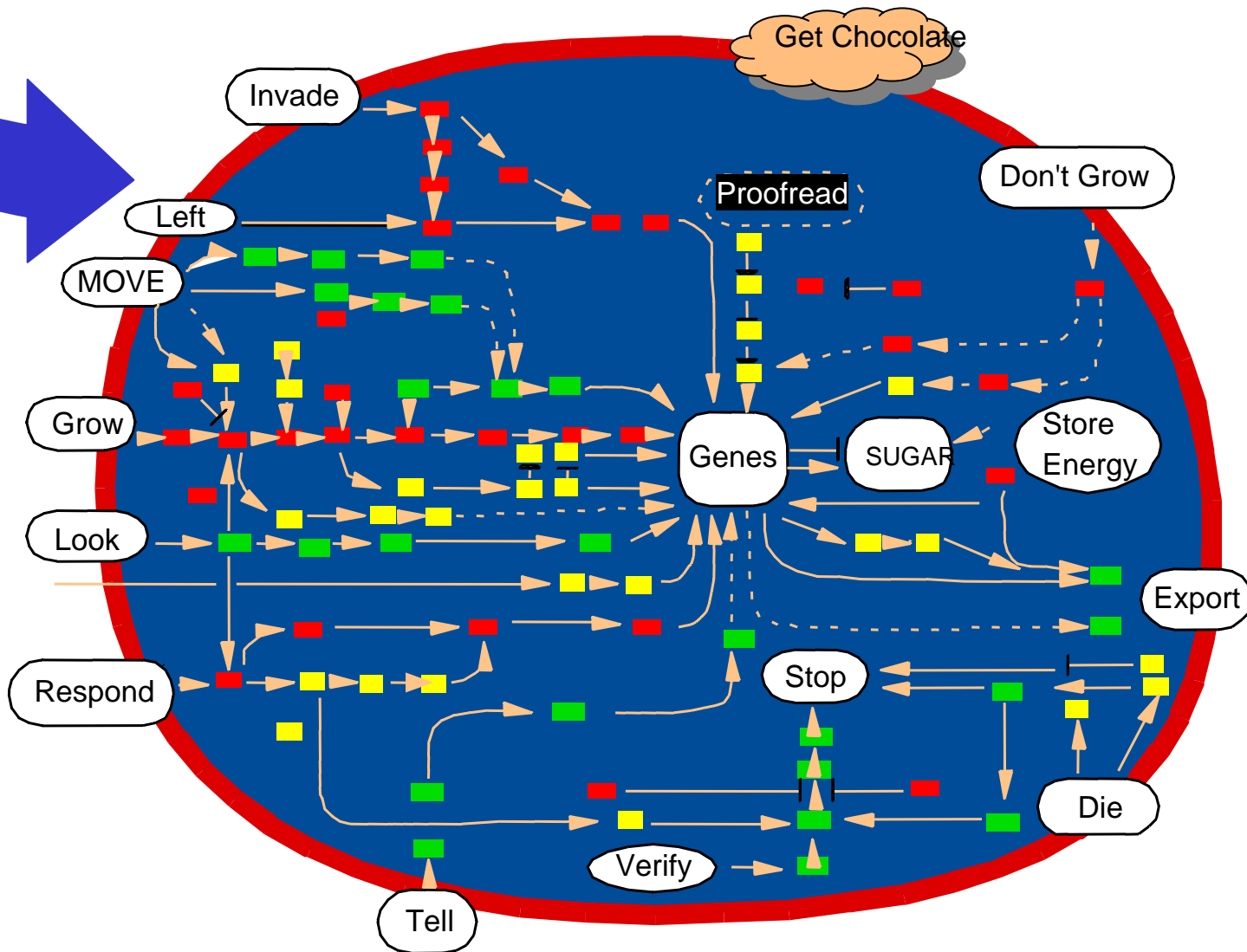
# Comparison of Four Model Animals for Genetic Analysis

<b>Animal</b>	<b>Adult Size (cm)</b>	<b>Genome Size (Mb)</b>	<b>Period of Organogenesis (d)</b>	<b>Generation Time (wk)</b>
<b>Nematode (<i>c. elegans</i>)</b>	<b>0.1</b>	<b>97</b>	<b>0.2-0.4</b>	<b>0.4</b>
<b>Fruit Fly (<i>Drosophila</i>)</b>	<b>0.4</b>	<b>180</b>	<b>0.5-1</b>	<b>2</b>
<b>Zebrafish</b>	<b>3</b>	<b>1,700</b>	<b>1-4</b>	<b>12</b>
<b>Mouse</b>	<b>6</b>	<b>3,000</b>	<b>6-15</b>	<b>10</b>
<b>Human</b>	<b>170</b>	<b>3,500</b>	<b>14-6</b>	<b>1400</b>

# Molecular Circuitry



# Cell Signaling Circuits



# Systems Biology Approach

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- Quantitative evaluation, through both laboratory experiments and computer simulation, of the manner in which the components of biological organisms are organized together to maintain normal physiological function.

# **NIEHS-ACC Collaborative RfA**


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## Developmental Toxicology Exploratory Research

- To stimulate research on the mechanism of action of developmental toxicants using the state of the art tools of 'omics' and model organisms including transgenic and gene knock out genetic animal models.
  - Stimulate the interaction/collaboration of developmental toxicologists with developmental biologists, molecular biologists and geneticists in order to fully integrate these new research directions and to expand our knowledge on the mode of action of developmental toxicants.
  - 12 Grants (R21) were jointly awarded for 2002-2004.

Developmental  
Biology

Developmental  
Toxicology



# Developmental Toxicology in the 21st Century: Multidisciplinary Approaches using Model Organisms and Genomics

April 22-24, 2002 NIEHS, Research Triangle Park,  
NC



# Application of Genomics

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- New tool provides vast amount of information
  - Data deluge
  - Quality?
  - Need to connect molecular level information to organs, organisms, and functions of systems.
  - Need to understand how stressors and genetics interact to impair function and cause adverse consequences.

# MIAME: Towards Standards

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- Minimum information about a microarray experiment (MIAME)
  - Minimum information required to ensure that microarray data can be easily interpreted and that results derived from its analysis can be independently verified.
  - Establish a standard for recording and reporting microarray-based gene expression data, which will in turn facilitate the establishment of databases and public repositories and enable the development of data analysis tools.
    - *Science* 2002 October 18; 298: 539 (in Letters)
    - *Nature* 419, 323 (26 Sep 2002) Opinion
    - *Nature Genetics: volume 29 no. 4 pp 365-371*

# Outlook to the future<sup>2</sup>

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- Improve the interdisciplinary advances in toxicology by better linking databases of developmental toxicology, developmental biology, and genomics.
- Establish multidisciplinary outreach programs for the effective exchange of information and techniques related to the assessment of toxicity for risk assessment.

<sup>2</sup>*abstracted from Scientific Frontiers in Developmental Toxicology and Risk Assessment*

