

Conceptual Mechanistic Models for the IRIS Toxicological Review of Inorganic Arsenic

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Outline for Today's Presentations

- Background
- Approach to Systematic Review
- Hazard Identification
- **Conceptual Mechanistic Models**
- Toxicokinetics
- Dose-Response Methods

Outline for This Presentation

- **Conceptual Mechanistic Models**

- Background
- Identifying and evaluating evidence
- Building models
- Considering susceptibility and other response modifiers
- Informing dose-response modeling

Background

Both MOA & AOP are terms used to describe conceptual mechanistic models



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Adverse Outcome Pathway (AOP) says:

This is a biological perturbation that can lead to a specific adverse outcome and here is how we think it happens.

Mode of Action (MOA) says:

Available data indicate that this AOP is relevant to a specific chemical of interest.



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Background

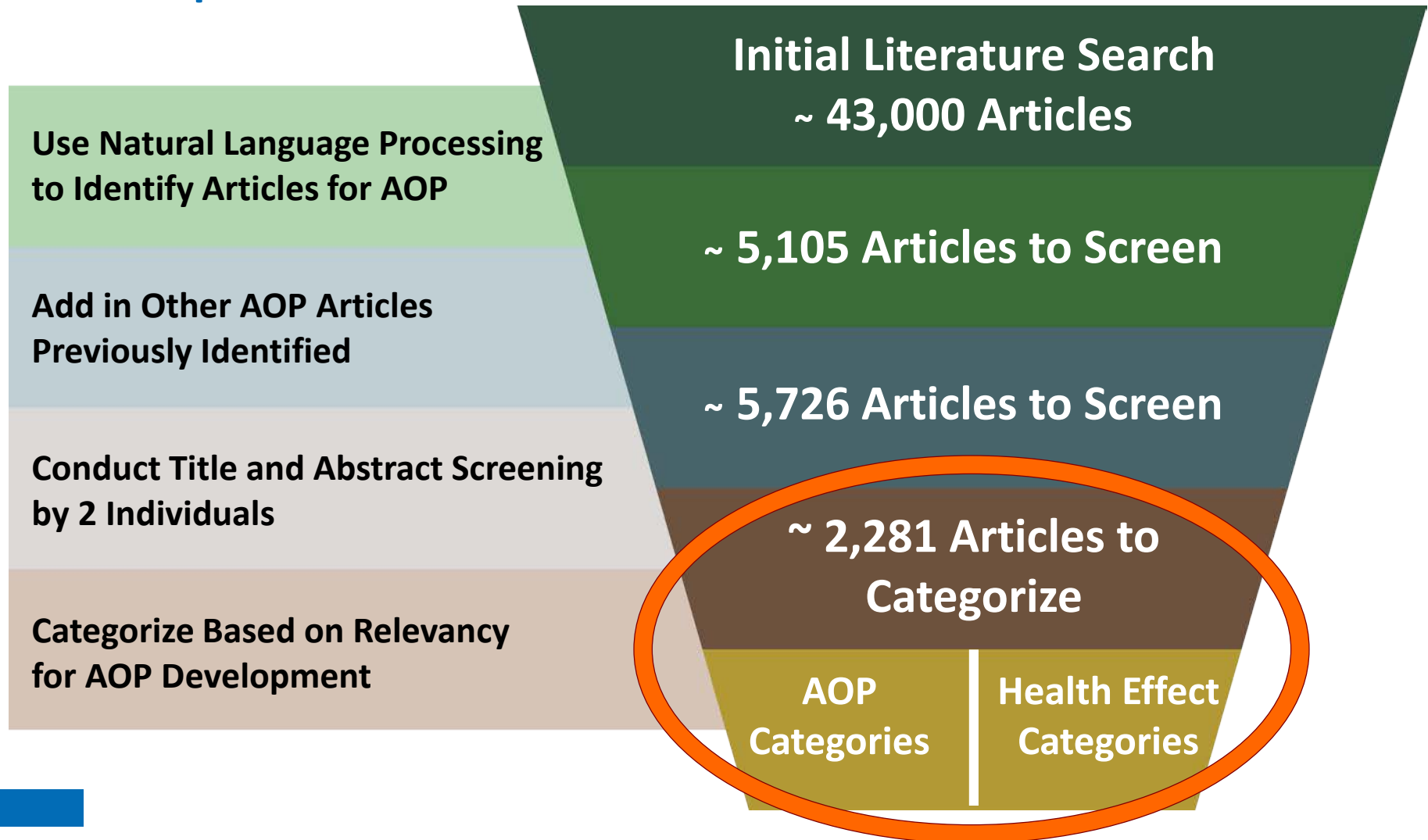
We Chose the Term AOP because it...

- Harmonizes among 34 Organization for Economic Co-operation and Development (OECD) member countries
- Utilizes a broader set of disease and natural biology data
- Provides potentially better understanding of the interaction of inorganic arsenic with response modifiers
- Better addresses a number of NRC recommendations



Identifying Arsenic-Specific Evidence

Comprehensive Literature Search



Identifying Arsenic-Specific Evidence

~ 2,281 Papers into 2 Broad Categories

Health Effect Specific	AOP Specific
102 Bladder	218 ADME
116 Cardiovascular	426 Cell viability, Proliferation, Cycle Changes
81 Developmental	86 Cellular Differentiation, Malignant Transformation
21 Digestive System	354 Gene Expression Changes
70 Endocrine System / Diabetes	96 Immune Mechanisms
88 Hematopoietic System	75 Endocrine Mechanisms
152 Immune System/Lymphatic	100 Epigenetic Mechanisms
266 Liver	241 Non-Oxidative DNA /Chromosomal Damage
122 Nervous System	29 Specific Proteotoxicity
93 Renal	653 Oxidative Stress Effects
84 Reproductive & Pregnancy	17 Regenerative Proliferation
110 Respiratory	95 Vascular Mechanisms
171 Skin	240 Other AOP
504 Cancer	
Categories not mutually exclusive	

Additional Sources of Evidence

National Institutes of Health National Library of Medicine

National Center for Biotechnology Information

BioSystems is a curated, public repository of disease-related pathways and networks (biological systems) and their component genes, proteins, and small molecules
(Pan et al. 2014; Geer et al. 2010)



Gene Expression Omnibus (GEO) is a curated, public, functional genomics data repository supporting MIAME (Minimal Information About a Microassay Experiment) compliant data submissions and is a source of gene expression profiles (Barrett et al 2013)



Evaluating Evidence

How do we evaluate evidence for AOP development?

Currently screening studies for “reliability” using criteria from:

- EUs Toxicological data Reliability Assessment Tool (**ToxR Tool**); applies to in vivo and in vitro data
(Segal et al 2015; Schneider et al., 2009)
- Systematic Omics Analysis Review (**SOAR**) Tool; applies to microarray and RNASeq data
(McConnell et al. 2014)

Evaluating Evidence

Example criteria

In Vivo Criteria from ToxR tool

- Was the test substance identified?
- Is the species given?
- Is the administration route given?

In Vitro Criteria from ToxR tool

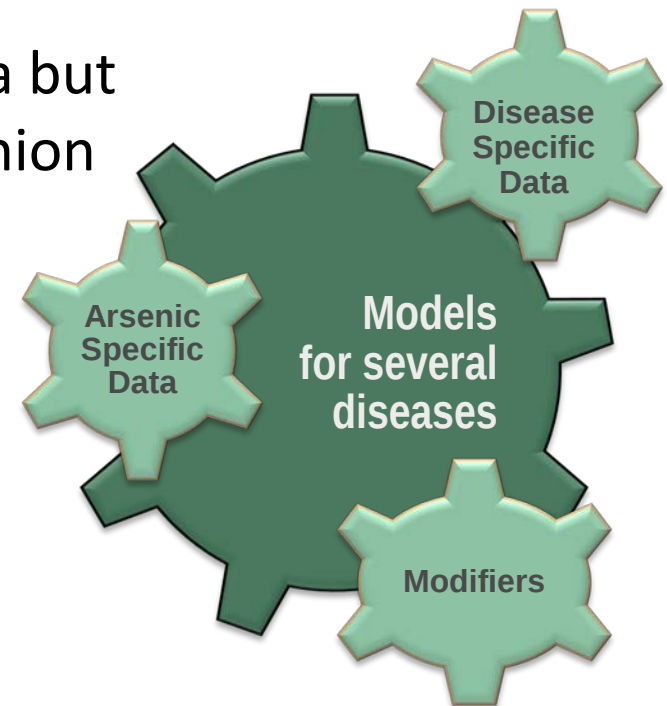
- Are doses administered or concentrations in application media given?
- Are frequency and duration of exposure and time points of observations explained?
- Is the study design chosen appropriate for obtaining the substance-specific data aimed at?

Microarray Specific Criteria from SOAR

- Does the microarray experiment include biological replicates?
- Is the microarray portion of the study performed in vivo or in vitro?
- Is the genetic material used in the microarrays taken from humans in vivo?

Building Mechanistic Models

- **We needed a framework to:**
 - Organize and synthesize lots of disparate data
 - Examine mechanistic commonalities among diseases and response modifiers, including susceptibility factors
 - Help capture not just qualitative data but quantitative data in a systematic fashion
- **We chose to utilize NIH Biosystems models**



Steps in Model Building

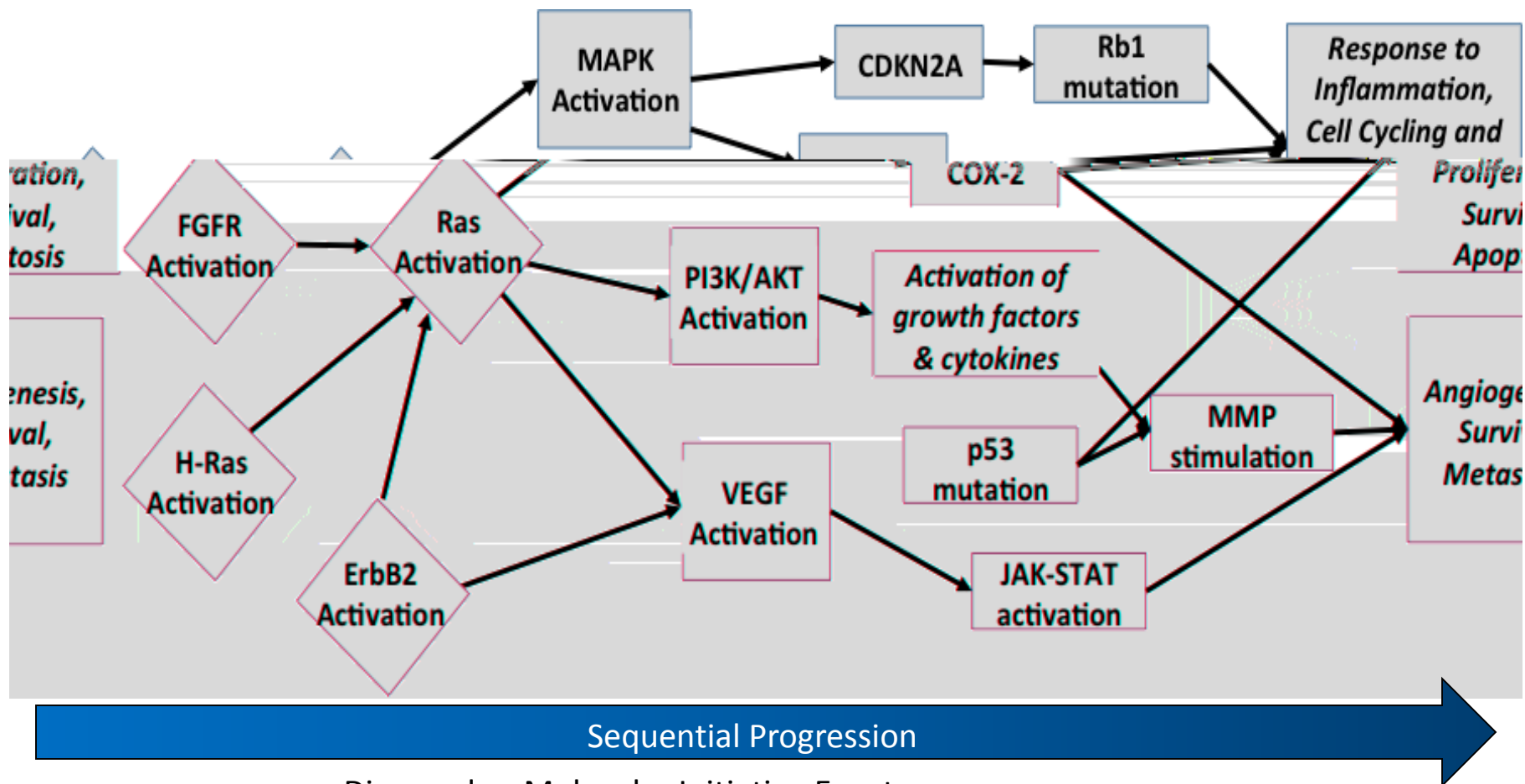
- **Step 1: Generate hypothesis**
 - Start with NIH Biosystems disease-specific models (v1)
 - Hand curate against current knowledge and update as needed
 - Models provides useful disease-specific framework for arsenic data
- **Step 2: Test hypotheses with arsenic-specific gene expression data**
 - Identify inorganic arsenic-specific, relevant* data in GEO
 - Keep only studies with raw data and reanalyze in consistent manner
 - Overlay arsenic gene expression data onto Biosystems models (v2)
 - Keep track of data not captured by models

*Mammalian, tissue-specific, in vitro, oral and inhalation routes of exposure data.

Steps in Model Building (cont.)

- **Step 3: Further elaborate the models with arsenic-specific data from other levels of biologic organization**
 - Overlay other arsenic data onto proposed models (v3)
 - Evaluate Steps 2 & 3 data not captured by models; potential modify
 - Diagram resulting models and tabulate underlying information including references and variables (e.g., test system, species, assays)
- **Step 4: Use models to better characterize common mechanisms across diseases and response modifiers**
 - Search for common mechanisms across diseases
 - Identify polymorphisms that may influence susceptibility
 - Identify mechanistic commonalities among risk modulators
- **Step 5: Inform dose-response models selection** (more later)

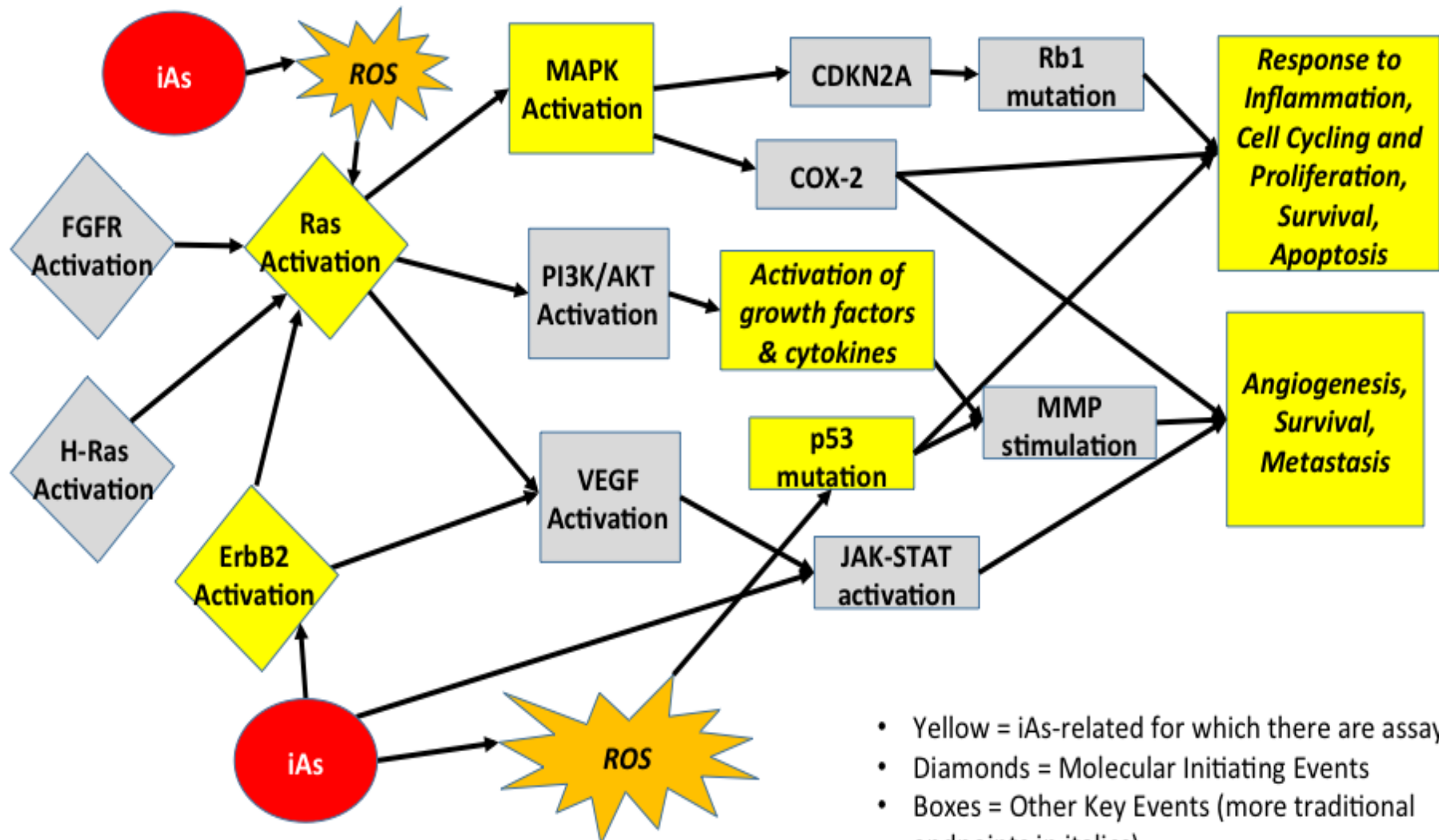
NIH BioSystems - Bladder Cancer (Partial) *Human (hsa05219)*



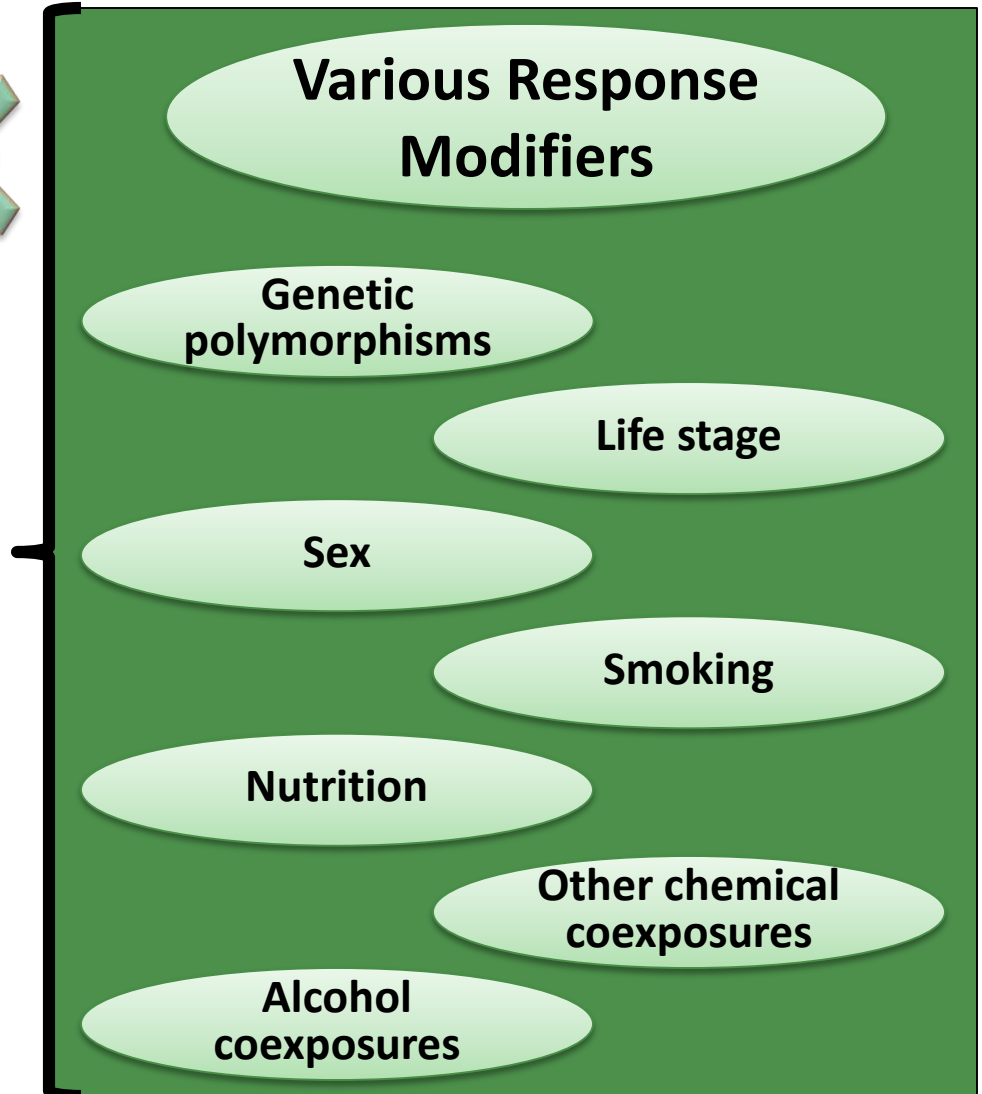
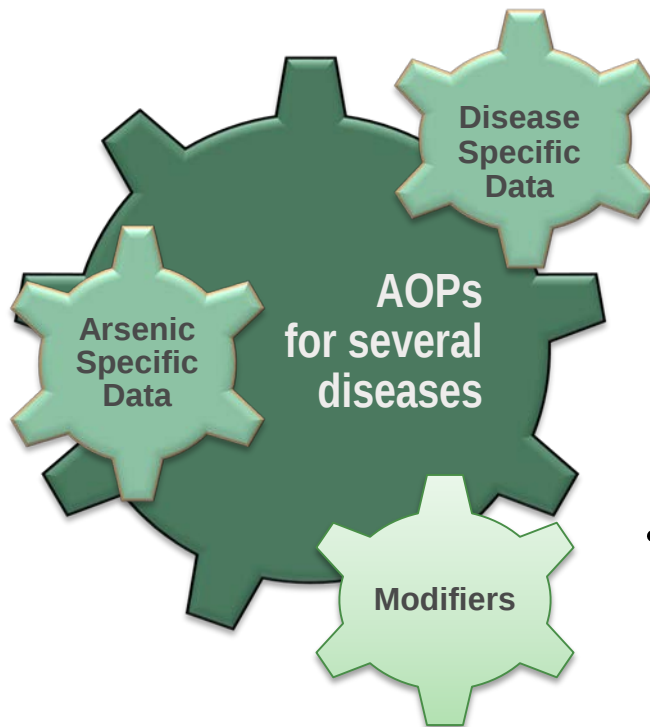
- Diamonds = Molecular Initiating Events
- Boxes = Other Key Events (more traditional endpoints in italics)
- <http://www.ncbi.nlm.nih.gov/biosystems/83115>

NIH BioSystems - Bladder Cancer (Partial)

Illustrative Annotation - Subset of Arsenic Data

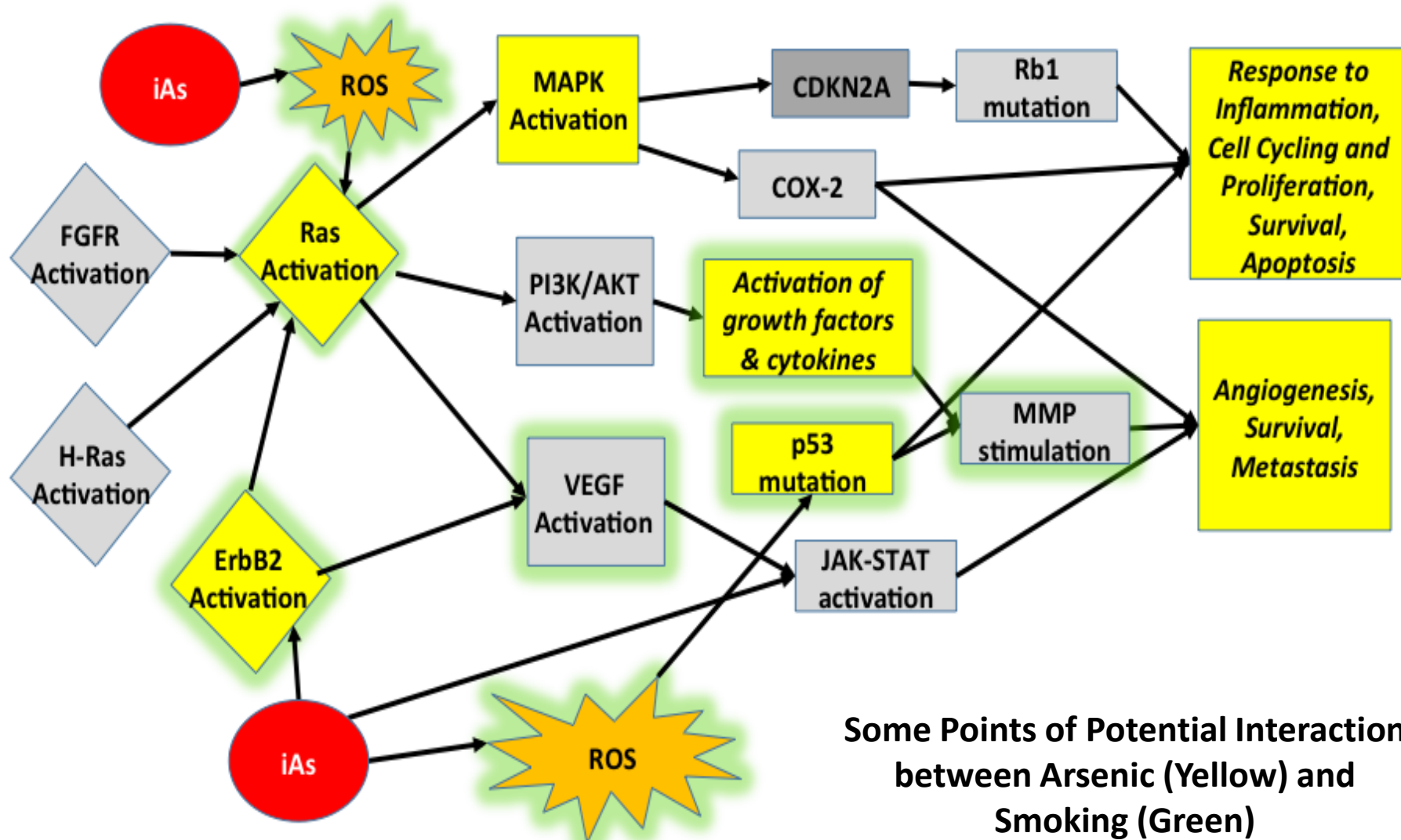


Considering Susceptibility and Other Response Modifiers

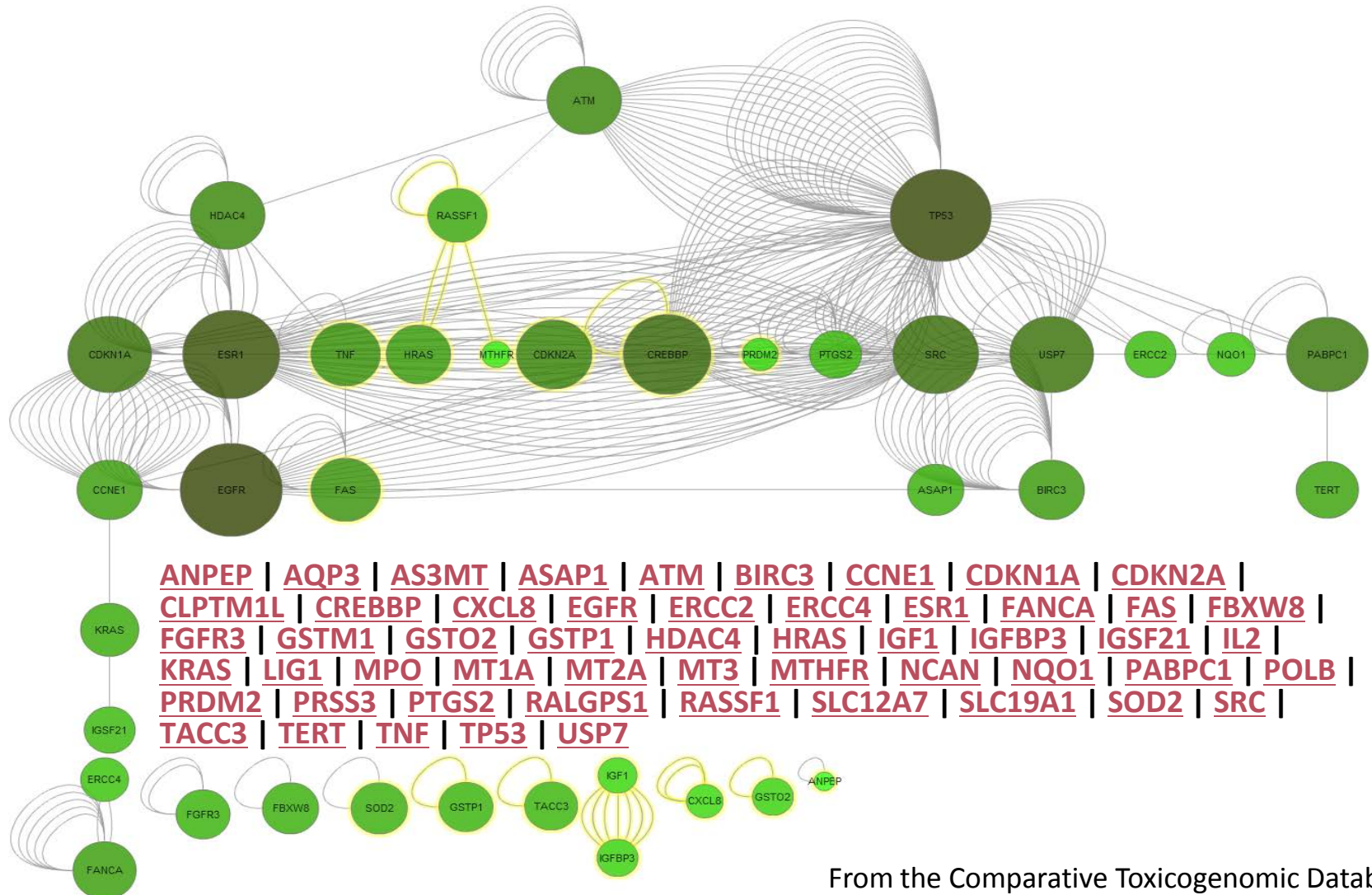


NIH BioSystems - Bladder Cancer (Partial)

Illustrative Annotation- Subset of Arsenic & Smoking Data



Other Possible Genes and Interactions for Arsenic-Related Bladder Cancer



From the Comparative Toxicogenomic Database

Potential Impacts of Mechanistic Information on Dose-Response Analyses

- **Evaluation of overall confidence in the selected model(s)** – Qualitative
- **Dose metric selection** – e.g., Importance of cumulative vs maximum dose (duration vs concentration), target organ
- **Response metric selection** – Identification of key precursor effects, selection of appropriate Bench Mark Response (BMR) level
- **Model weighting** – Assigning prior weights to model forms in a Bayesian model averaging approach
- **Parameter priors** - Assigning prior probabilities (or constraints) to model parameters in a Bayesian MCMC analysis
- **Sensitivity analyses** - Factors such as background exposure, dosimetry, and risk modifiers

Summary: Conceptual Mechanistic Models

- We have a system for identifying and evaluating mechanistic information
 - We are building qualitative models using both disease- and chemical- specific data for a variety of endpoints
 - We are capturing quantitative data as we go.
 - We think these models will help us better interpret the data in terms of
 - causality
 - response modifiers
 - potentially dose-response considerations
- 
- A decorative graphic in the bottom right corner consisting of a semi-circular arrangement of various blue icons. These icons represent different fields of science and technology, including a microscope, a beaker, a globe, a computer monitor, a book, a gear, a lightbulb, a DNA helix, and a rocket. The icons are densely packed and overlap, creating a complex, circular collage.



Acknowledgements

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