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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

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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

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.

Slide courtesy of Dan Villeneuve

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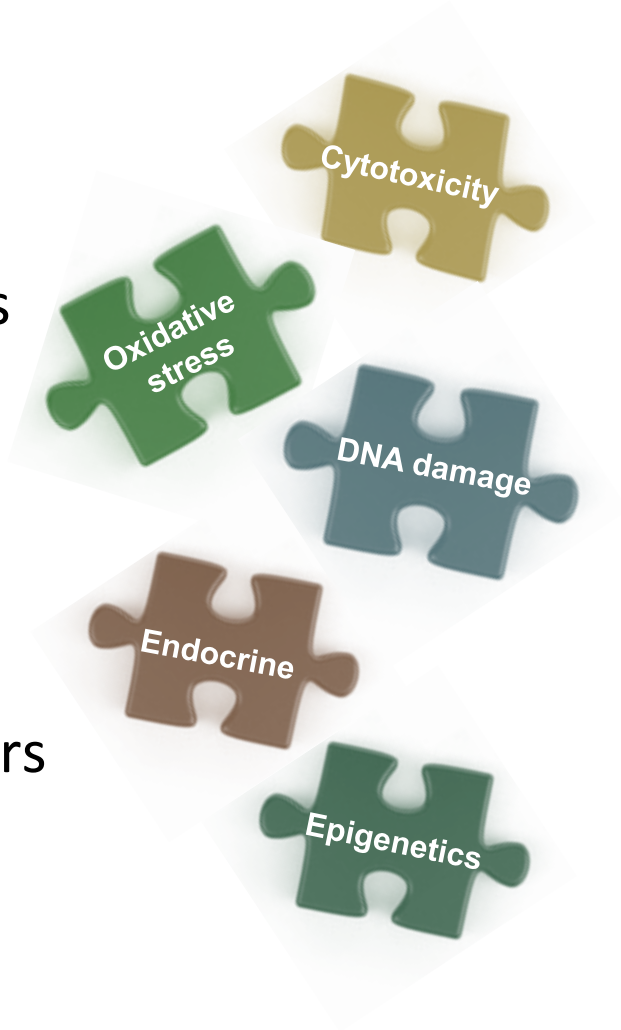
Background

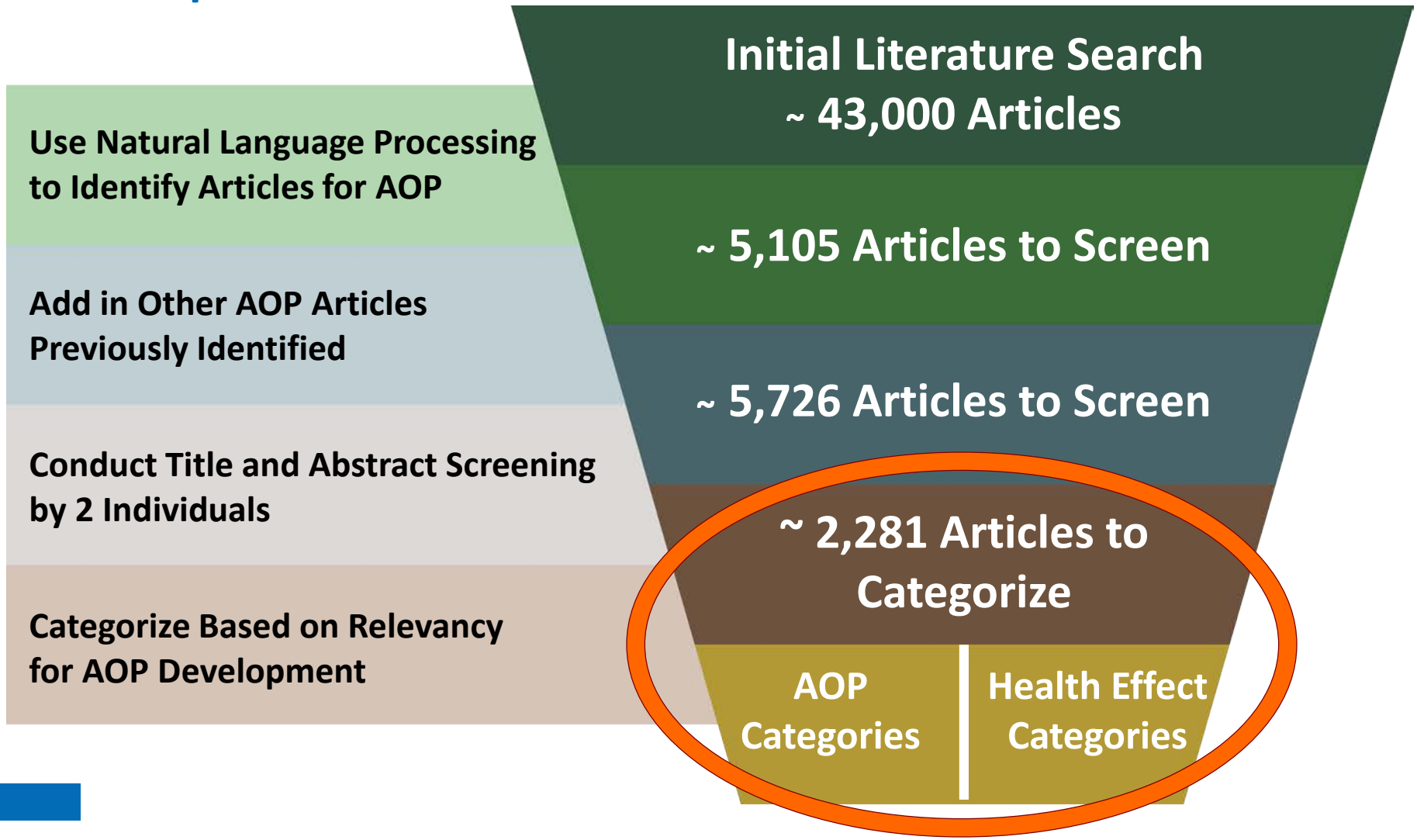
We Chose the Term AOP because it…

- 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



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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)

Gene Expression Omnibus

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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)

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Evaluating Evidence
Example criteria

In Vivo Criteria from ToxR tool
- Was the test substance identified?
- Is the species given?
- Is the administration route given?

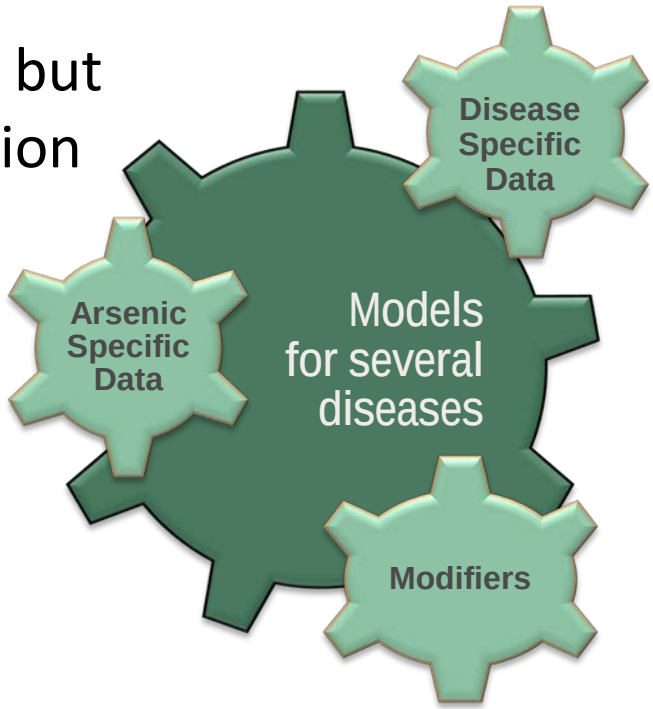
In Vitro Criteria from ToxR tool
- Are doses administered or concentrations in application media given?
- Are frequency and duration of exposure and time points of observations explained?
- Is the study design chosen appropriate for obtaining the substance-specific data aimed at?

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?

From Segal et al. 2015 (from ToxRTool) and McConnell et al. 2014 (from SOAR)

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**



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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

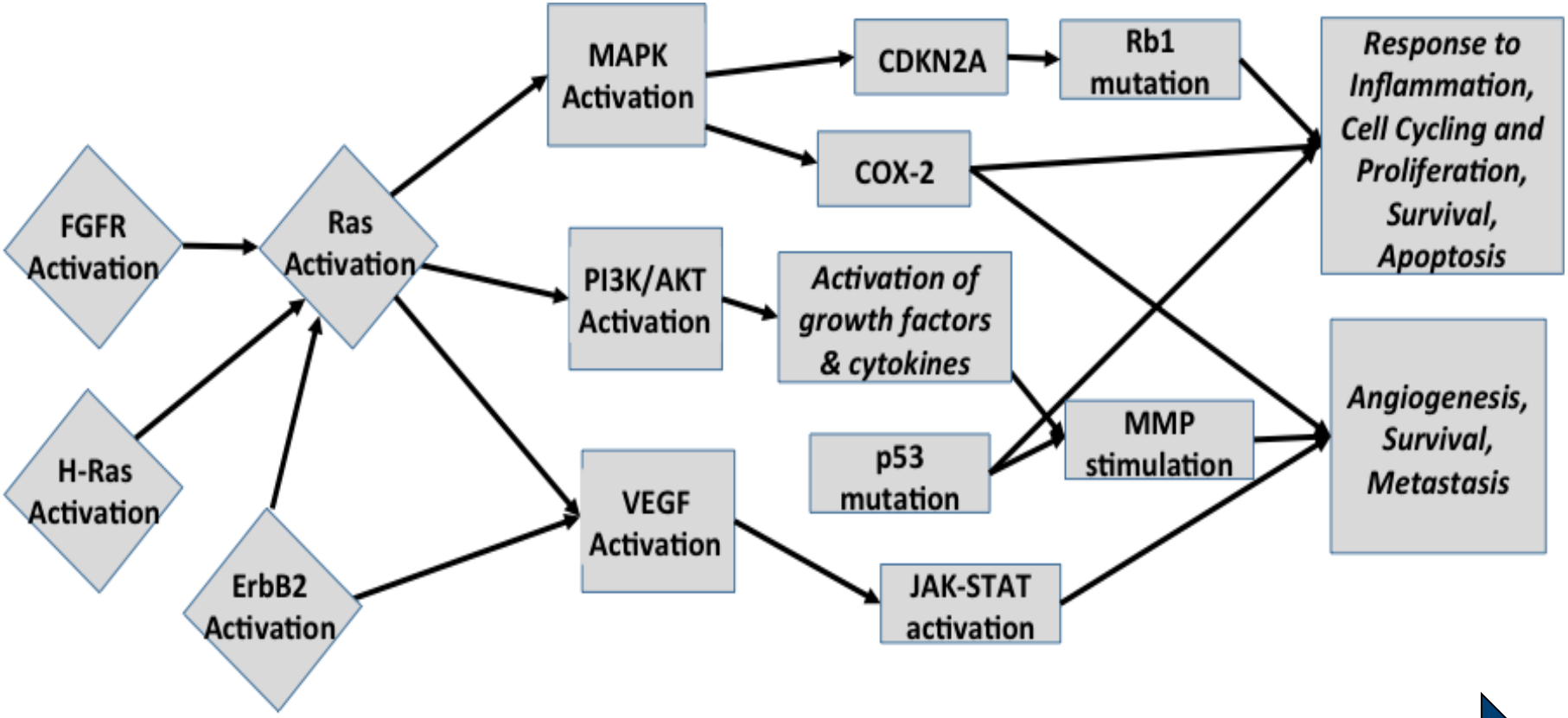
*Mammalian, tissue-specific, in vitro, oral and inhalation routes of exposure data.

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

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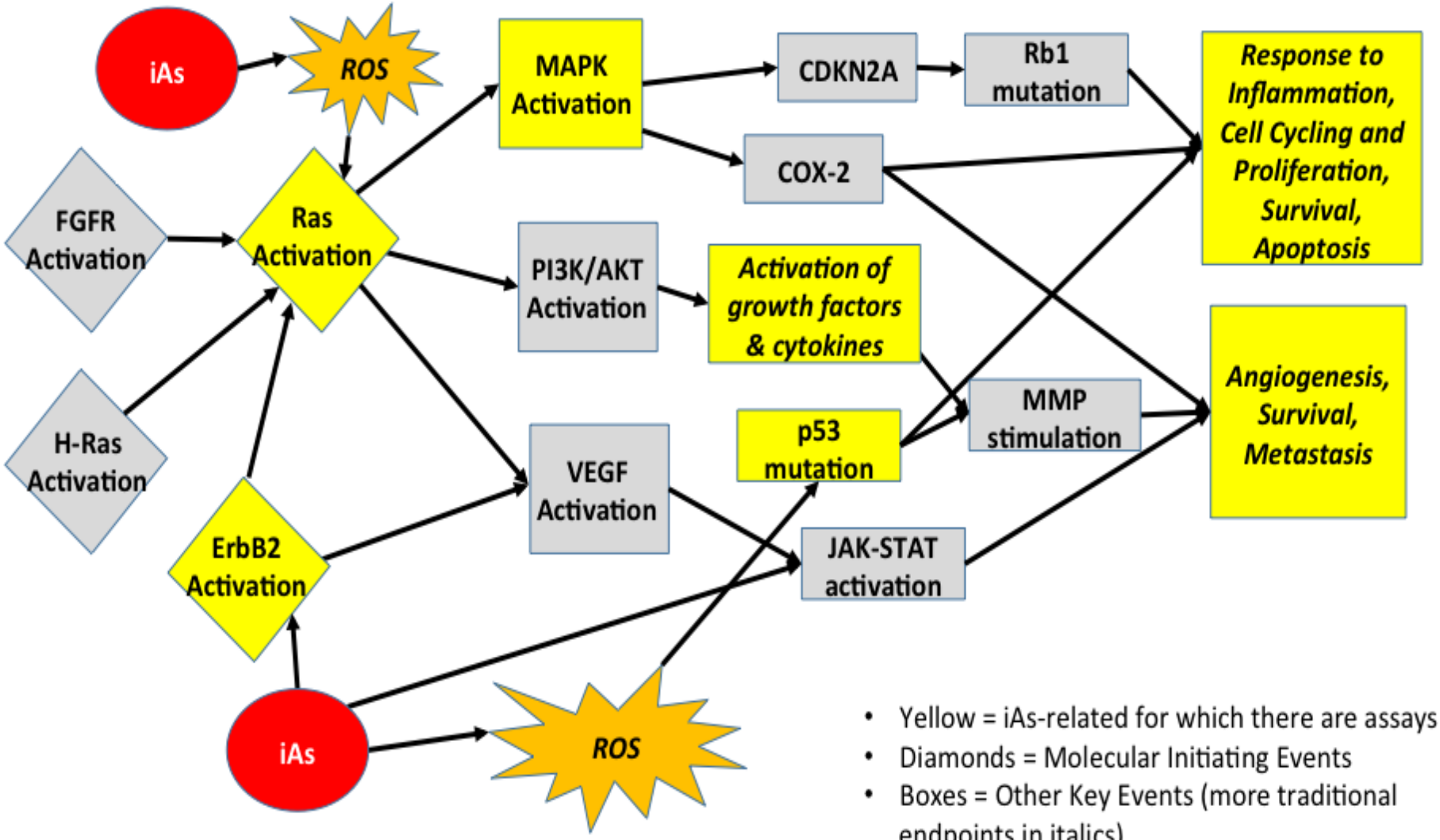
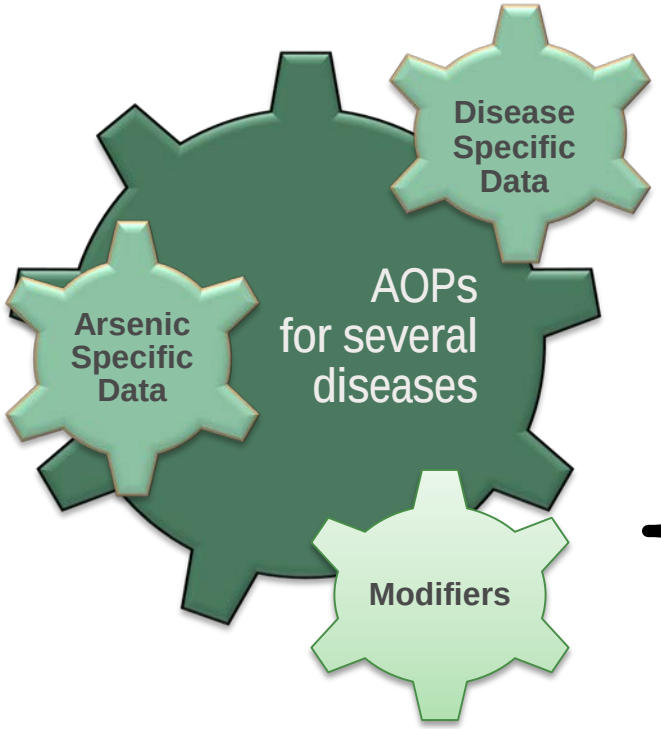
NIH BioSystems - Bladder Cancer (Partial)

Illustrative Annotation - Subset of Arsenic Data



- Yellow = iAs-related for which there are assays
- Diamonds = Molecular Initiating Events
- Boxes = Other Key Events (more traditional endpoints in italics)

Considering Susceptibility and Other Response Modifiers



- Various Response Modifiers
  - Genetic polymorphisms
  - Life stage
  - Sex
  - Smoking
  - Nutrition
  - Other chemical coexposures
  - Alcohol coexposures

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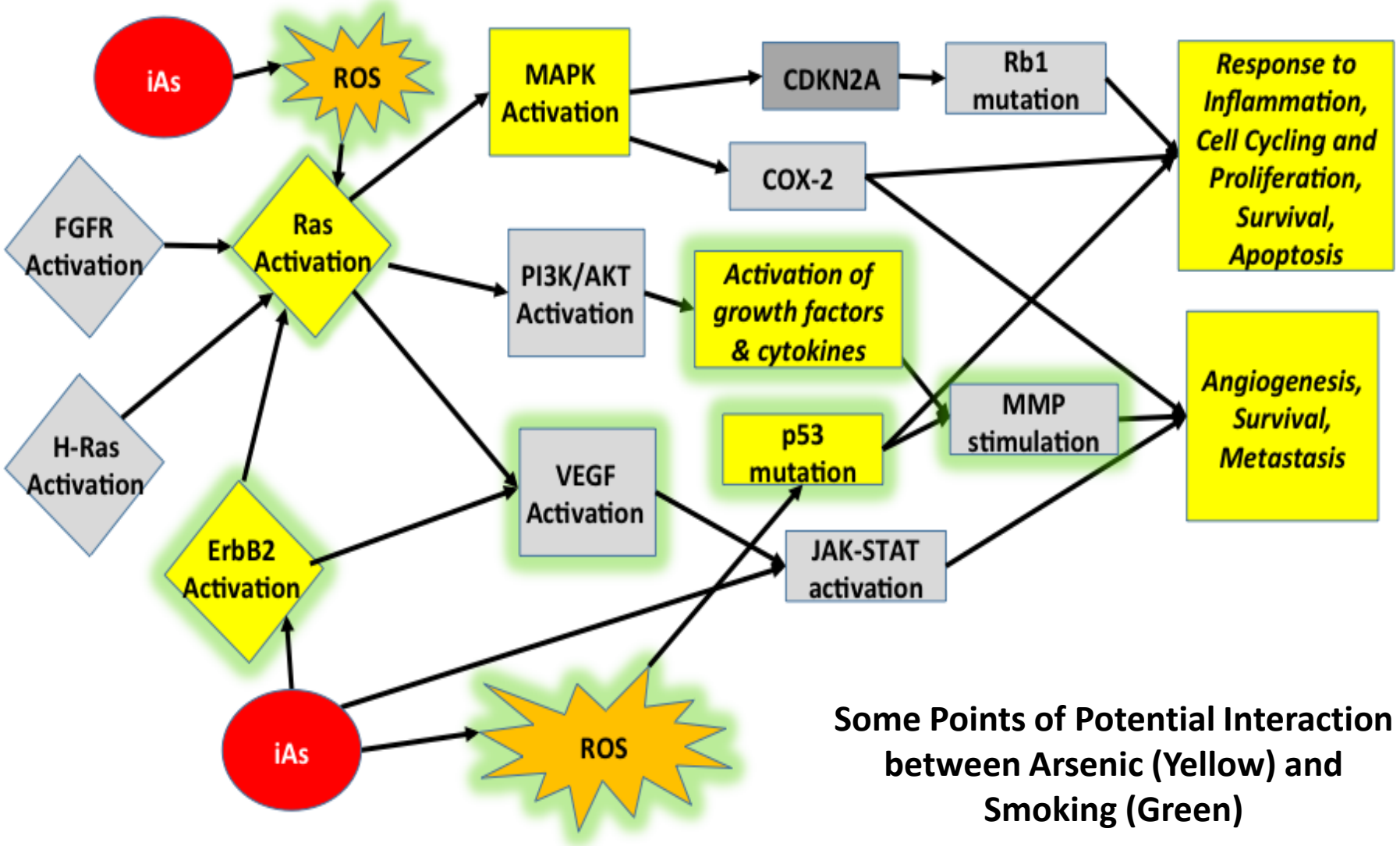
NIH BioSystems - Bladder Cancer (Partial)

Illustrative Annotation- Subset of Arsenic & Smoking Data



Some Points of Potential Interaction between Arsenic (Yellow) and Smoking (Green)

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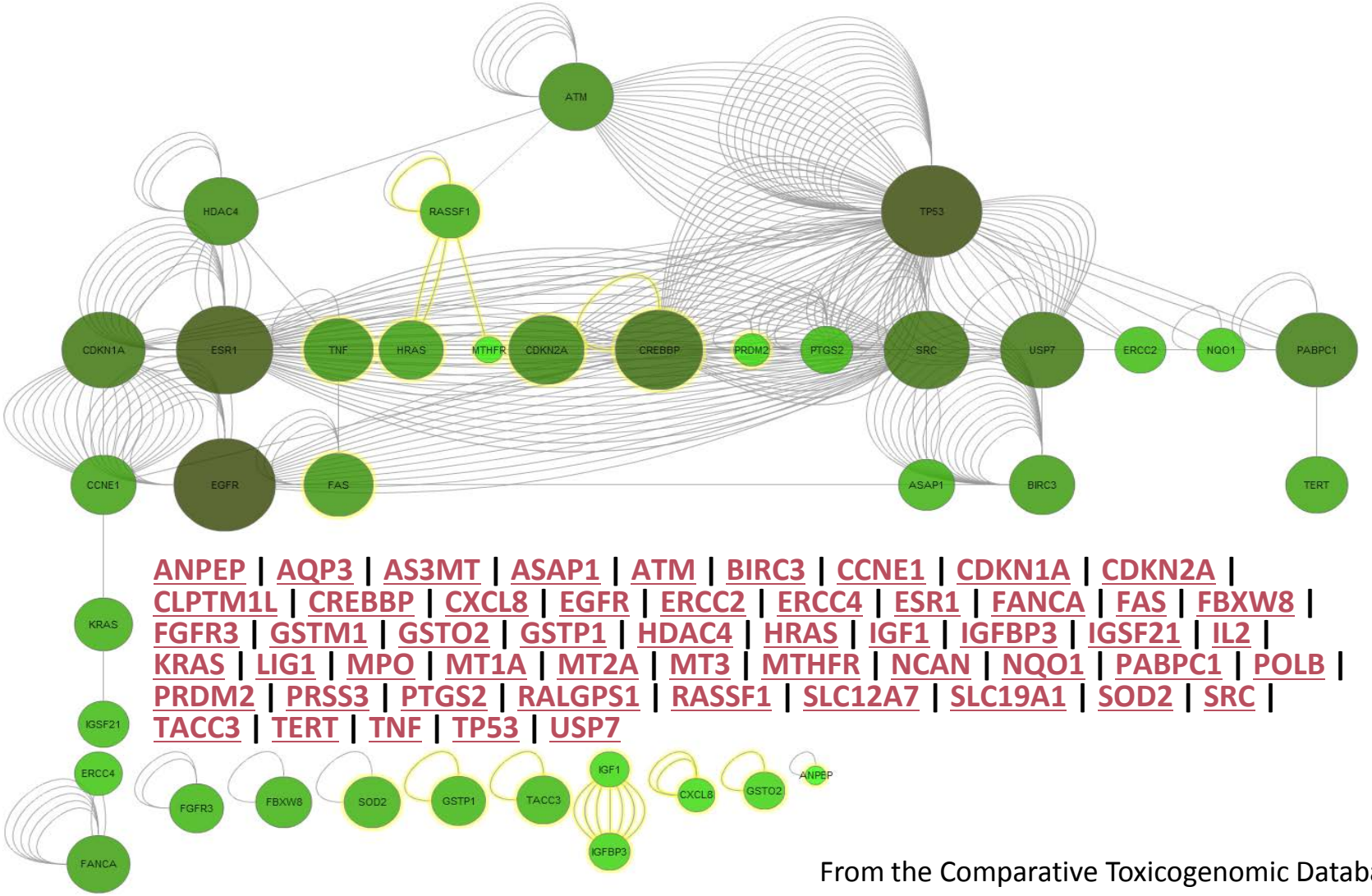
Other Possible Genes and Interactions for Arsenic-Related Bladder Cancer



ANPEP | AQP3 | AS3MT | ASAP1 | ATM | BIRC3 | CCNE1 | CDKN1A | CDKN2A | CLPTM1L | CREBBP | CXCL8 | EGFR | ERCC2 | ERCC4 | ESR1 | FANCA | FAS | FBXW8 | FGFR3 | GSTM1 | GSTO2 | GSTP1 | HDAC4 | HRAS | IGF1 | IGFBP3 | IGSF21 | IL2 | KRAS | LIG1 | MPO | MT1A | MT2A | MT3 | MTHFR | NCAN | NQO1 | PABPC1 | POLB | PRDM2 | PRSS3 | PTGS2 | RALGPS1 | RASSF1 | SLC12A7 | SLC19A1 | SOD2 | SRC | TACC3 | TERT | TNF | TP53 | USP7

From the Comparative Toxicogenomic Database

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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

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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

Figure courtesy of “censemaking”

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