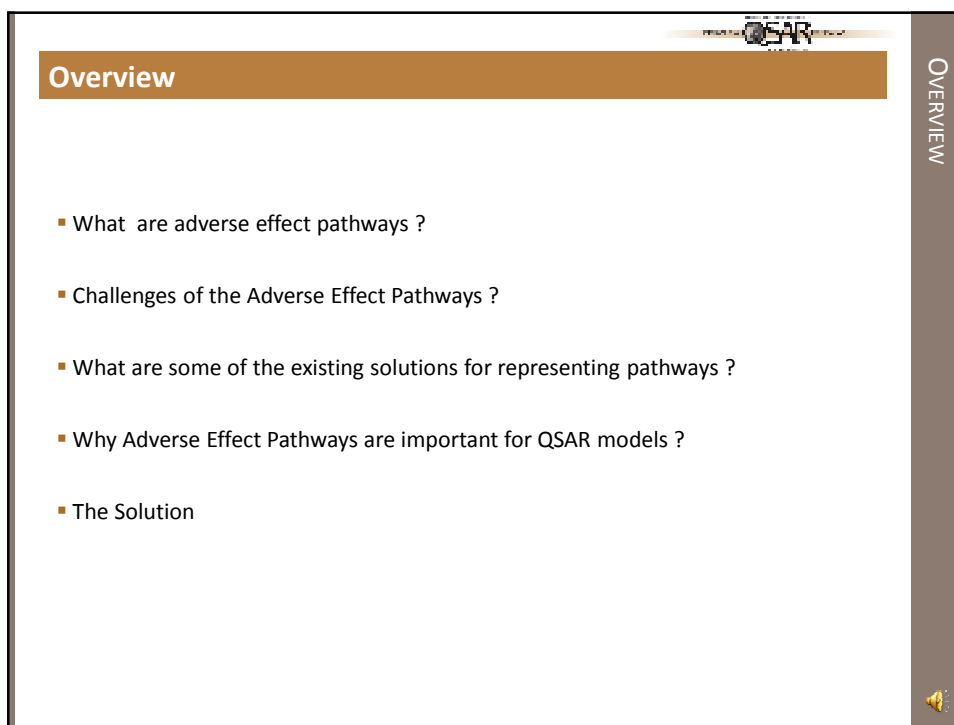


VISUALIZATION OF ADVERSE EFFECT PATHWAYS

Hristo Aladjov

QSAR Foundation

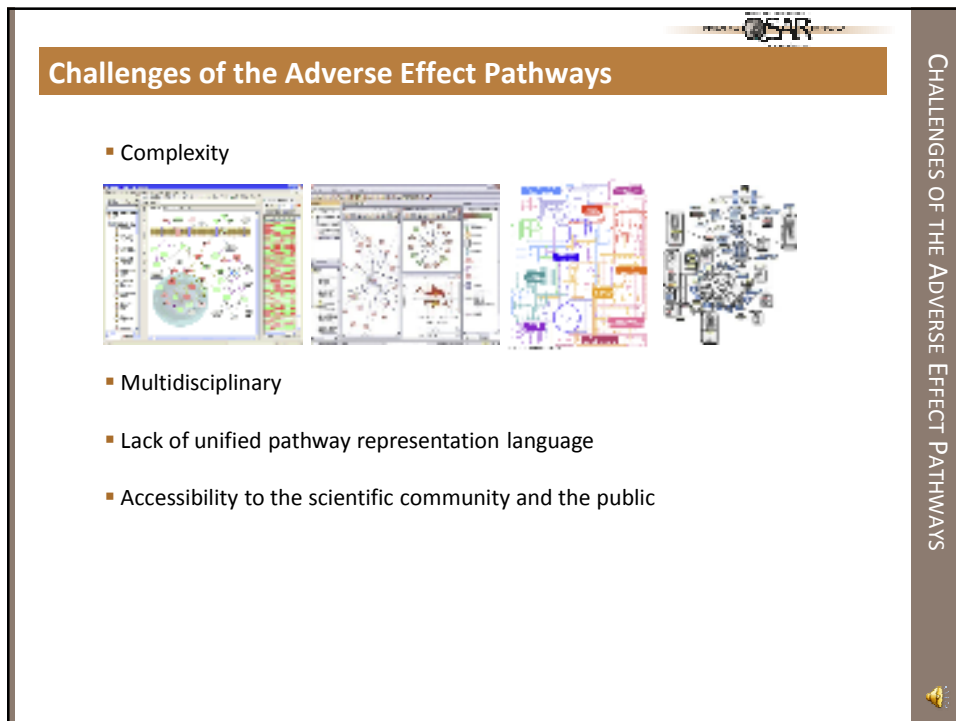
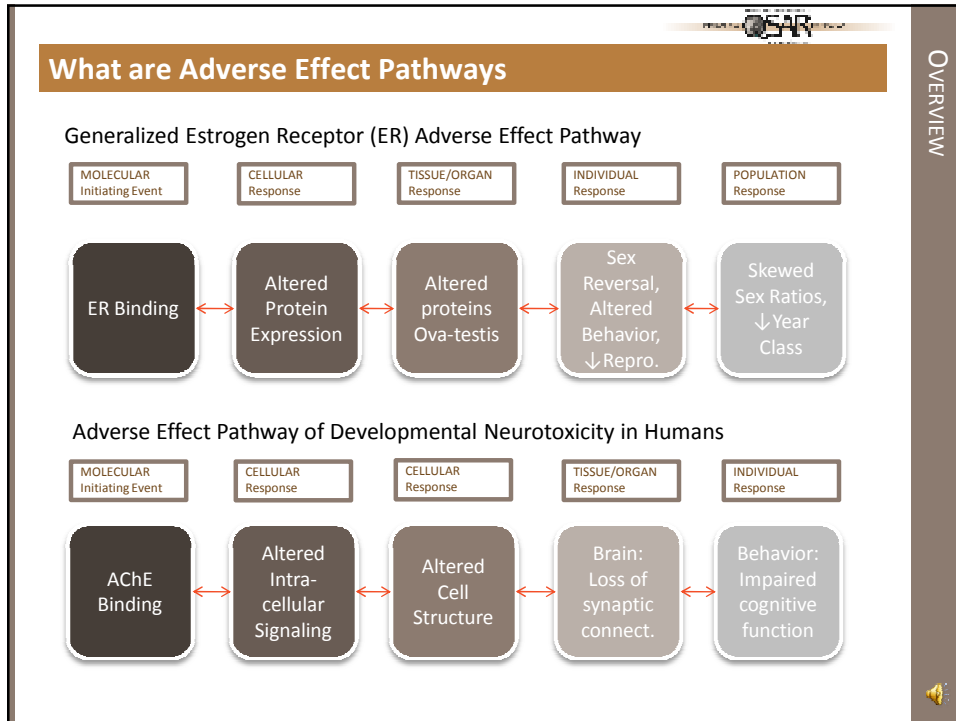


Overview

- What are adverse effect pathways ?
- Challenges of the Adverse Effect Pathways ?
- What are some of the existing solutions for representing pathways ?
- Why Adverse Effect Pathways are important for QSAR models ?
- The Solution

OVERVIEW

QSAR Foundation



## Existing Solutions

- System biology models advantages
  - Systematic description of the complex interactions in biological systems
  - Integrate and analyze complex data from multiple experimental sources
- System biology models disadvantages
  - Exhaustive complexity not focused by the subject of study
  - Focus on molecular level
  - Investigating the continuous uncompensated dysfunction
- ToxRefDB
  - Collection of endpoints
- ToxCast
  - Collection of in-vitro cellular assays



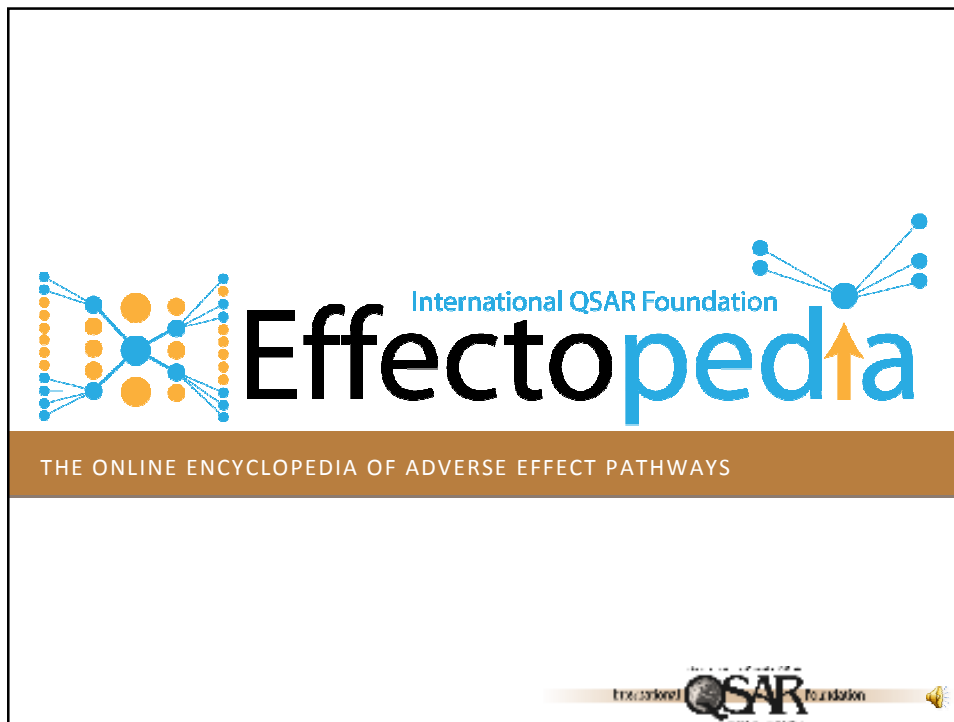
## QSAR models and Adverse Effect Pathways

- First Rule of QSAR:  
Select well defined Endpoint
- Model different mechanisms/modes of action separately
- Separate chemical models from biological effects
- Use transparent mechanistically interpretable methods
- Use good quality data



Inspiring the Next Generation  
QSAR Models,  
based on classic rules





**Effectopedia – Adverse Effect Pathways Representation System**

- Simple enough to make it manageable, complex enough to be useful
- Build the pathways from both ends
- Brake the complexity with simple questions
- Provide organized slots and global context for integrating individual experts knowledge
- Create efficient way of expert collaboration
- Create open standard for pathway presentation
- Make all data freely accessible online

EFFECTOPEDIA.QSARI.ORG

### Use Simple Building Blocks

```
graph LR; Cause[Cause] --> Link[Link]; Link --> Effect[Effect];
```

- Cause**
  - Chemical
  - Molecular Initiating Event
  - Effect
- Link**
  - Threshold
  - Dose-Response
  - Reversible or not
  - Specific or not
  - Duration
- Effect**
  - Molecular Initiating Event
  - Effect
  - Endpoint

PATHWAY BUILDING BLOCKS

### Coordinates in Pathway Space

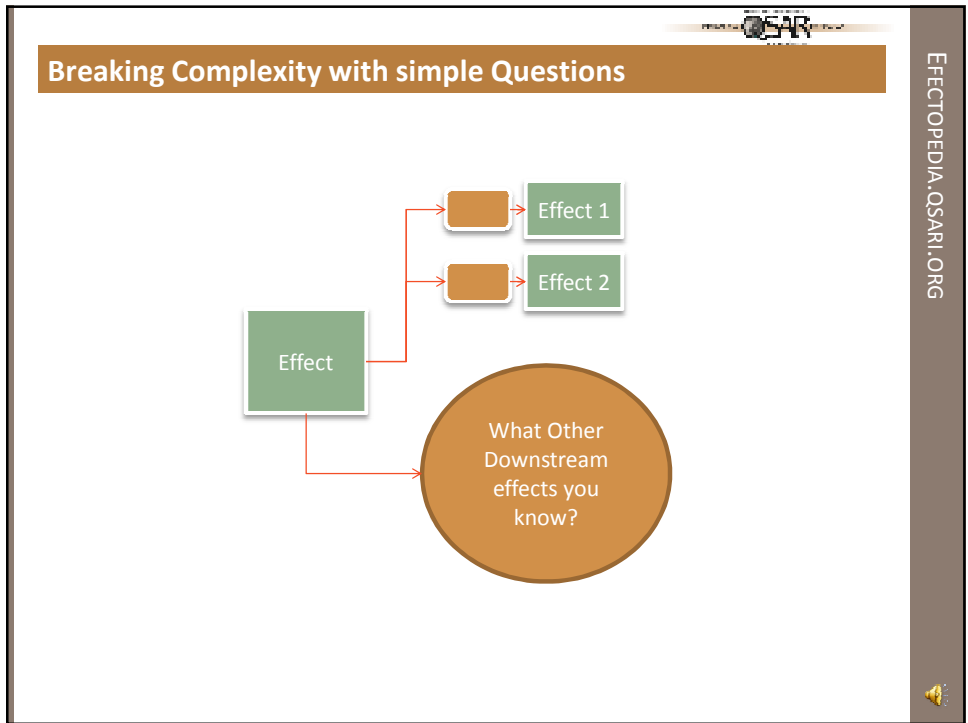
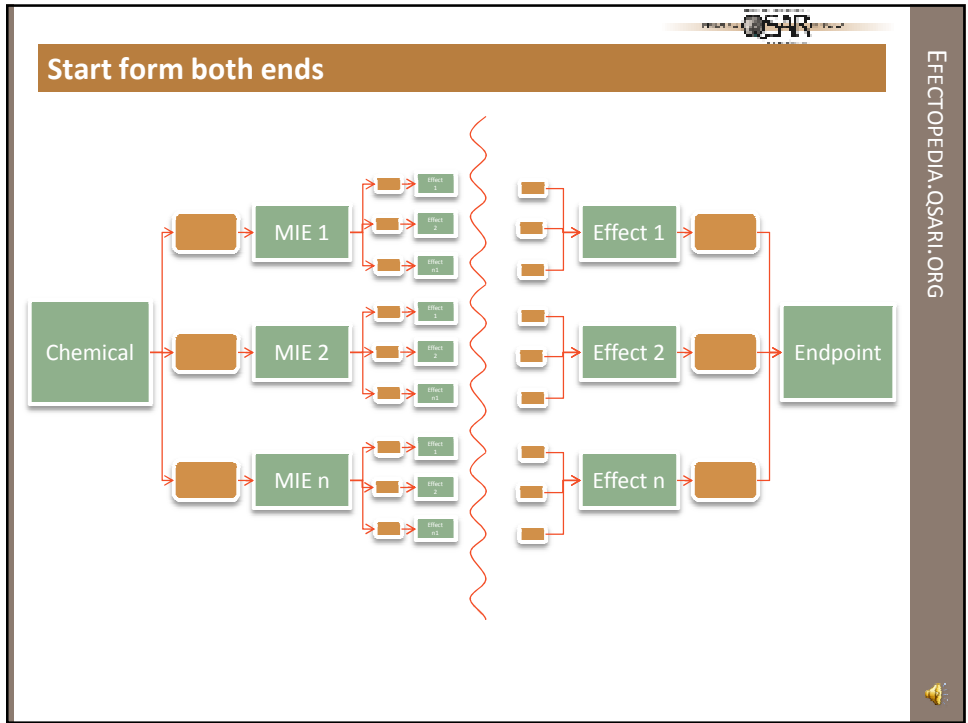
Effect:  
...  
male  
adult  
human  
Liver  
...

Gender

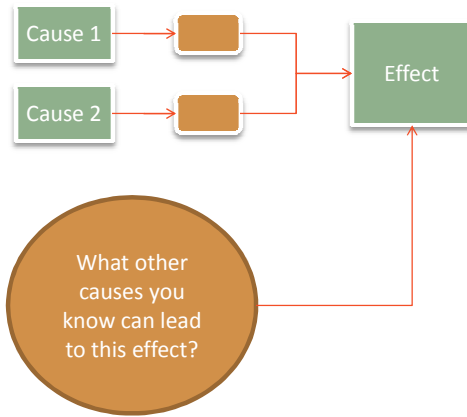
Life Stage

Taxonomy

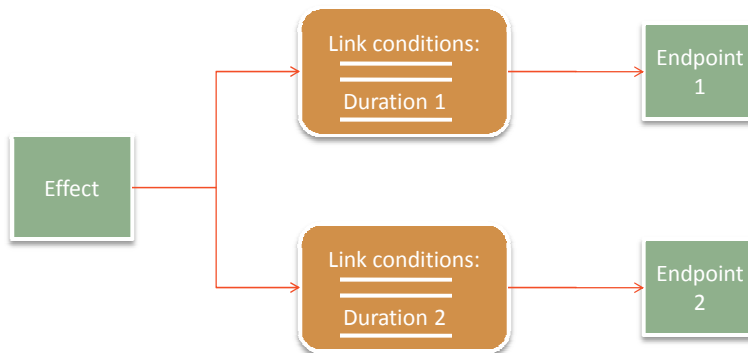
Level of Biological Organization



### Breaking Complexity with simple Questions

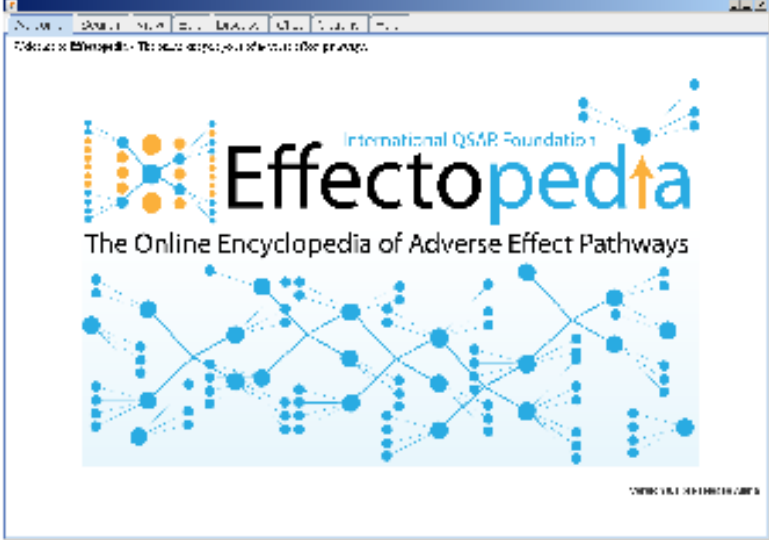


### Dysfunction Duration as a Cause



OSAR

## Demo





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OSAR

## Technology

- Based entirely on open source platform independent solutions

<? XML ?>

- Accessible with standard web browser
- Creates search engine optimized static HTML pages for higher visibility
- Standard XML based language for direct data import / export
- Modular, Plug-in architecture
- Open source

FREE, PLATFORM INDEPENDENT, OPEN SOURCE



QSAR

## Benefits

- QSAR models can be used for what they are good for – predicting molecular initiating events and identifying chemicals with similar behavior without additional animal testing
- Provide a global context and new applications of existing experimental data
- Create public knowledge repository that stimulate research and modeling efforts
- Outline the most frequently used tests in regulatory decision making process to facilitate the search for alternative methods.
- Help identify missing information and facilitate experiment design.
- Create focused and effective discussion environment

CONCLUSIONS

