



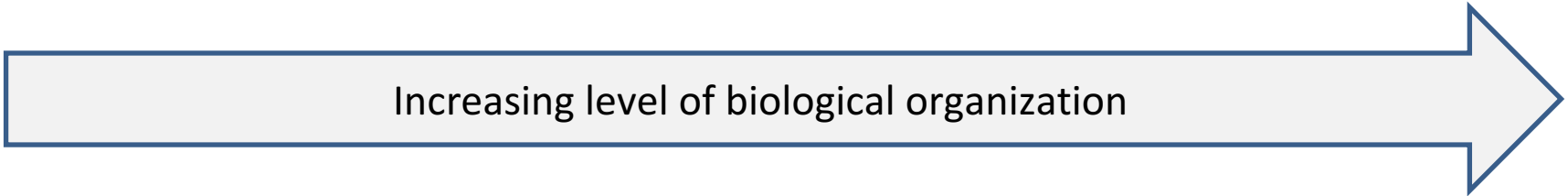
The European Commission's science and knowledge service

Joint Research Centre Creating and Using an AOP

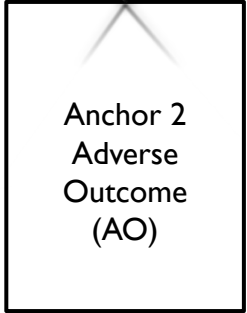
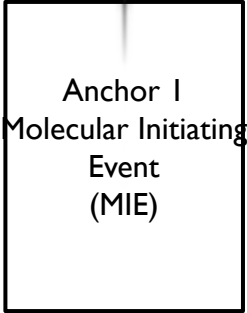
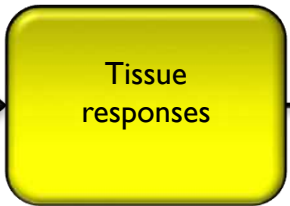
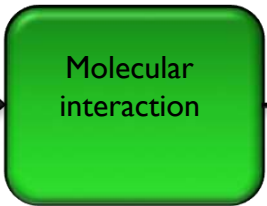
13th March 2018
Brigitte Landesmann

DISCLAIMER:

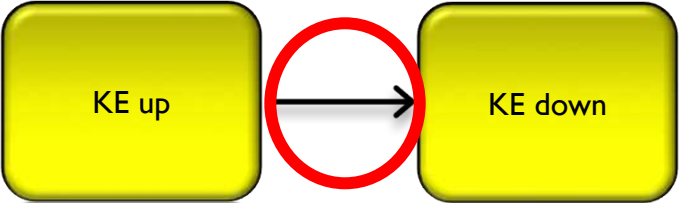
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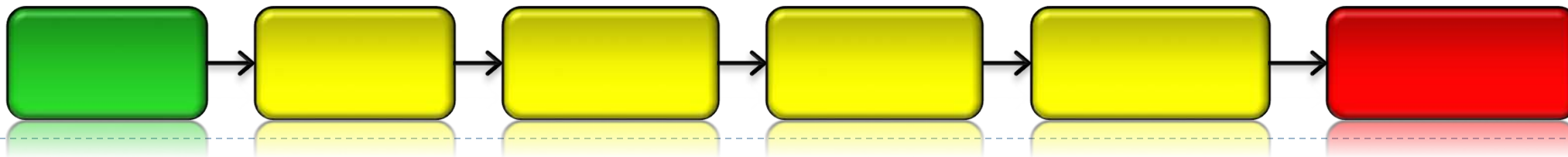


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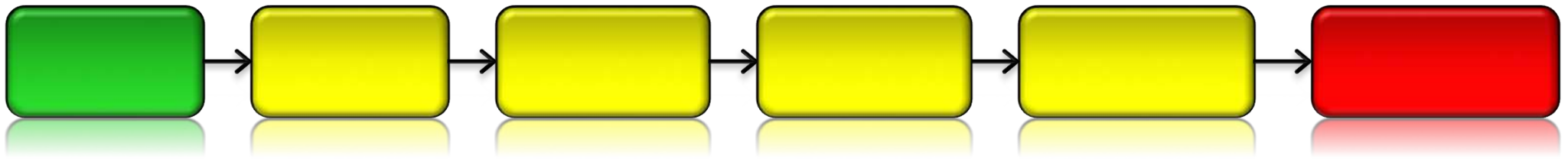
Key Event Relationships (KERs)





The Five Principles of AOP Development

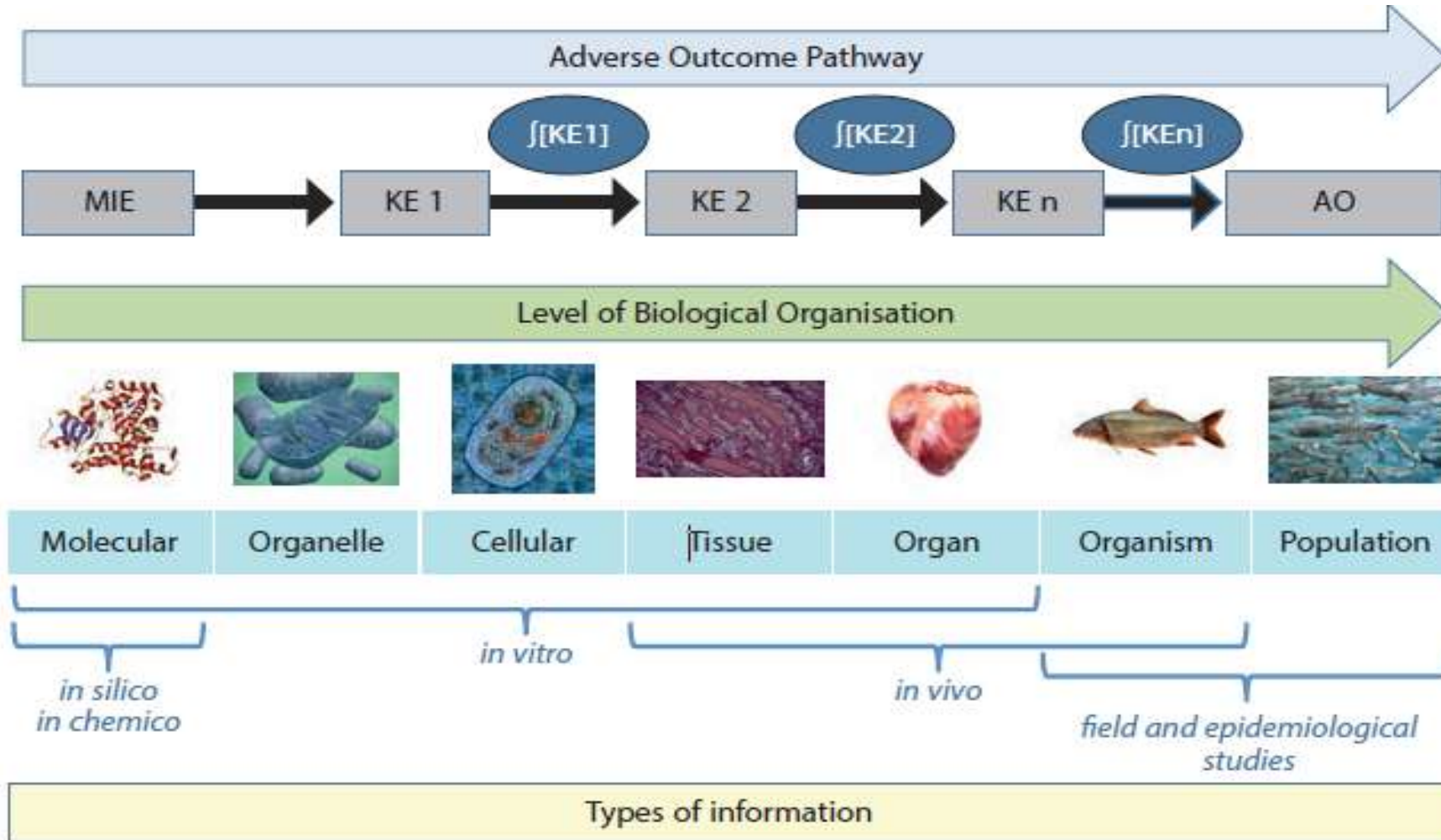
- ❖ AOPs are NOT chemical-specific
- ❖ AOPs are MODULAR
- ❖ AOPs are a pragmatic functional unit of development and evaluation
- ❖ AOP networks are the functional unit of prediction
- ❖ AOPs are living documents

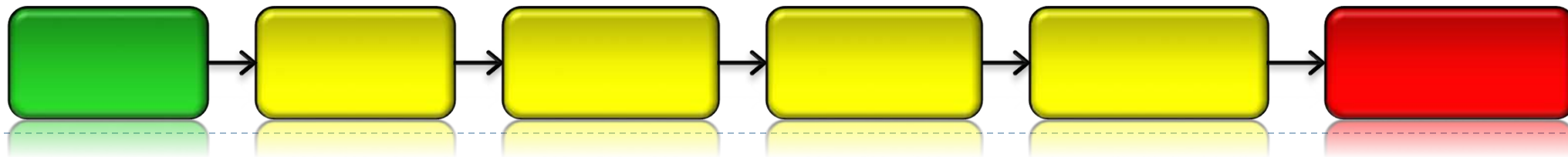


AOPs thrive because of the interactivity and multidisciplinary of the crowd



Collection and organisation of various types of information

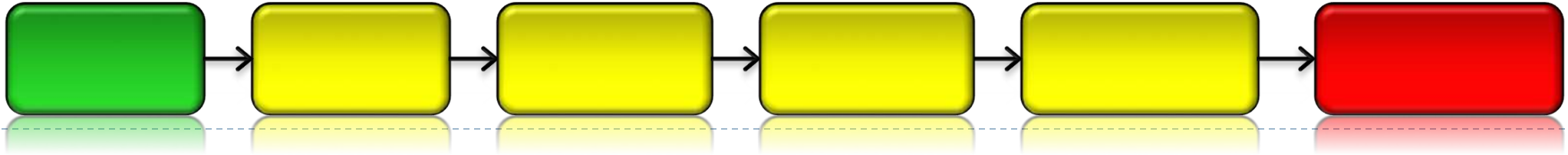




AOP and MOA

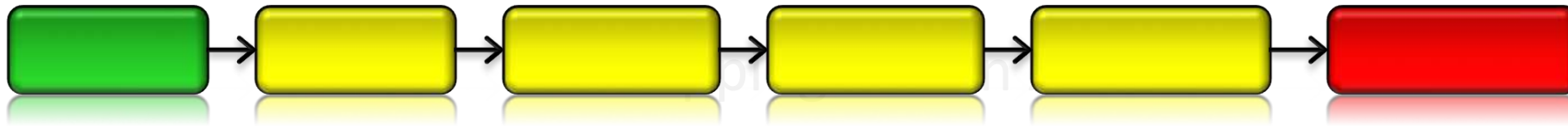
- ▶ **AOP:** chemical unspecific
- ▶ **MoA:** chemical specific





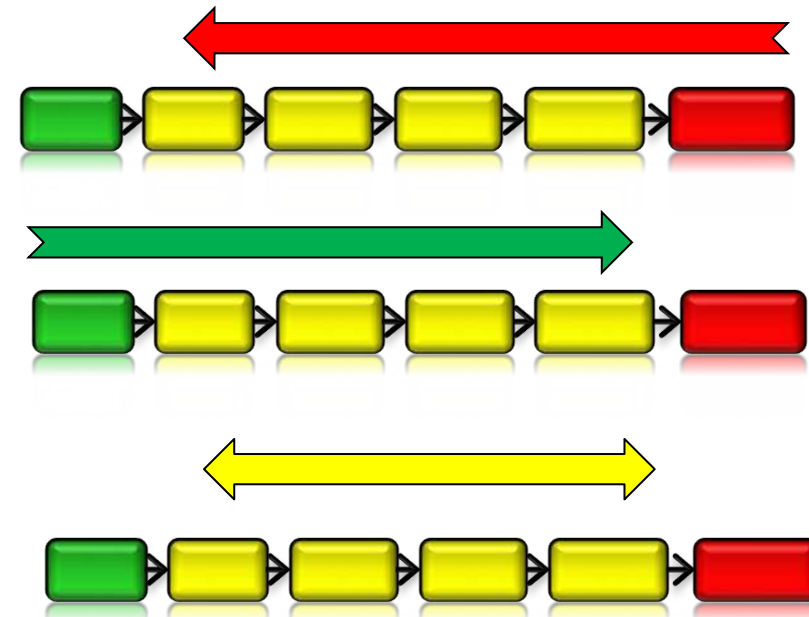
Building an AOP

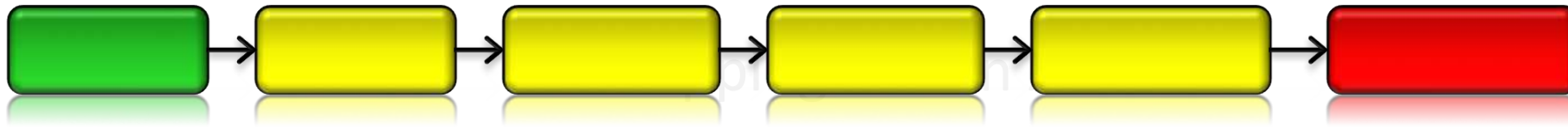




Q: Where to start?

- Top-down AOP development
- Bottom-up AOP development
- Middle-out AOP development





Q: What is the minimum number of elements that can constitute an AOP?

A: Three.

Q: What is the maximum number of KEs that can be included in an AOP?

A: In theory, there is no maximum number of KEs.

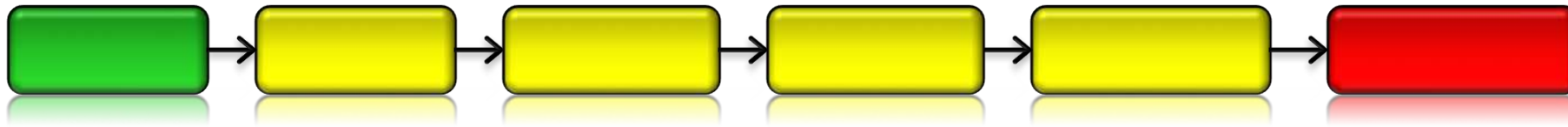
Q: How many KEs should be included in an AOP?

A: It depends

Convention:

- One MIE
- Desirably, one KE at each level of biological organization
- One AO (AOPs can have more than one AO)



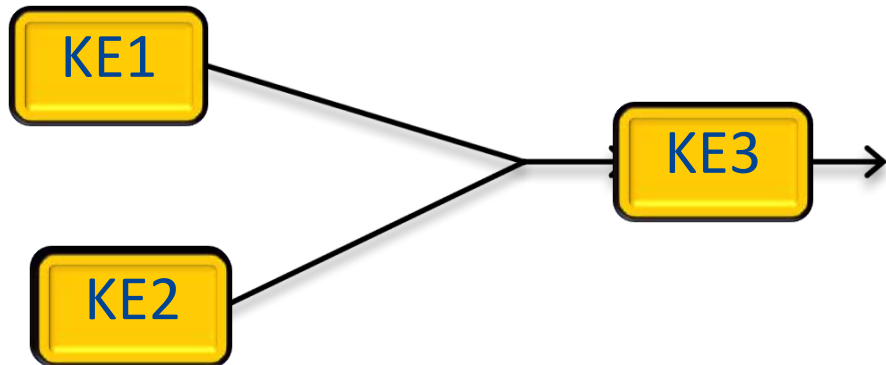


MIE:

- Typically one per AOP
- Can link to any number of separate AOPs

(rare) exception:

Two events **MUST** occur to trigger the downstream KE.

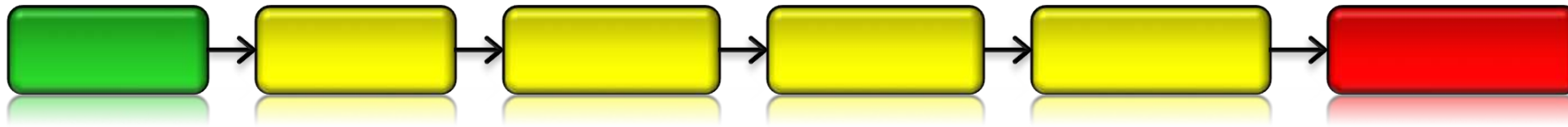


KE1 and KE2 must occur for KE3 to occur

not

KE1 or KE2 must occur for KE3 to occur



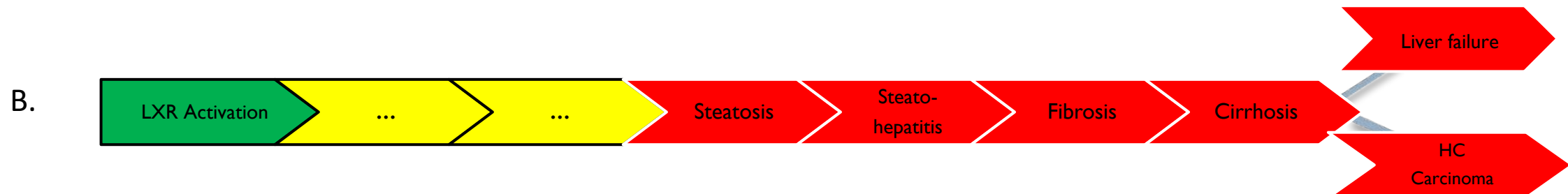


AO:

- Potentially more than one per AOP - if they represent a single progression of injury



Multiple AOs in a single, sequential progression = single AOP

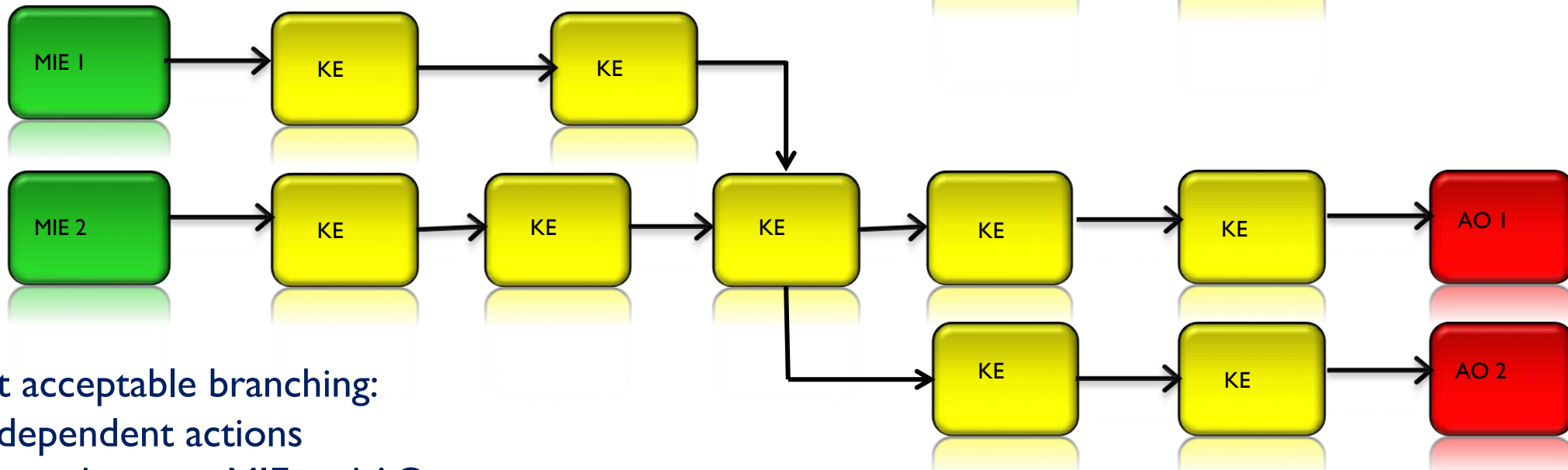
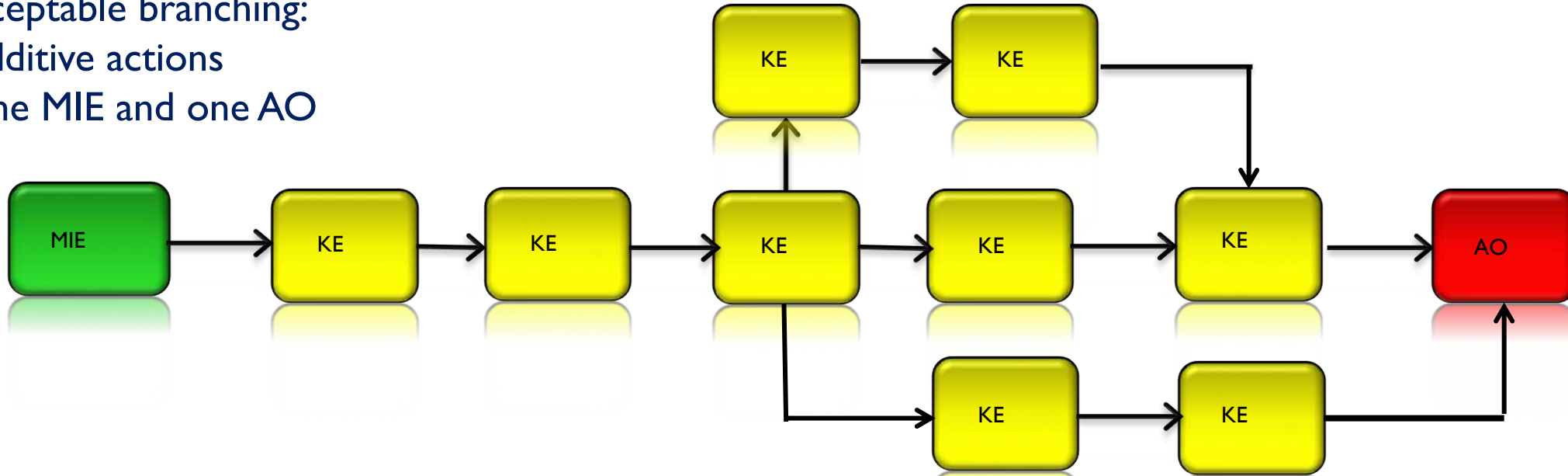


Branching = two AOPs



Acceptable branching:

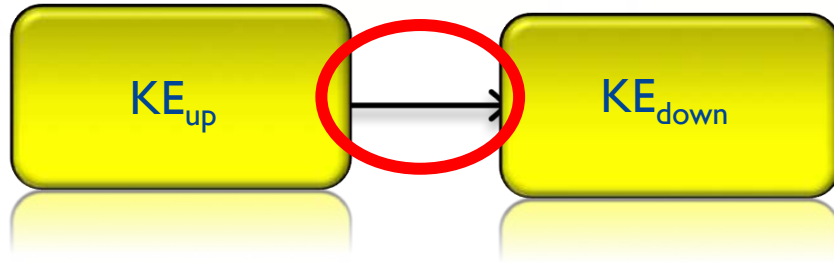
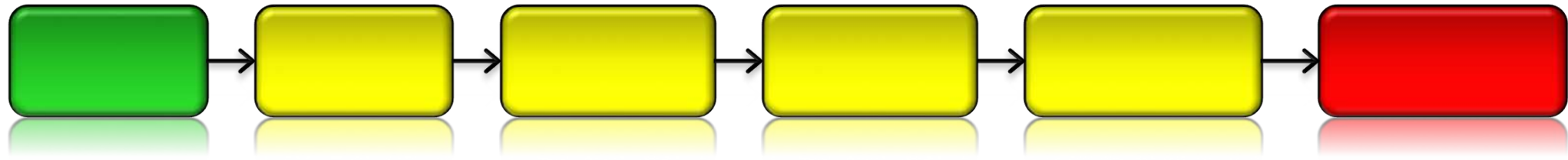
- additive actions
- one MIE and one AO



Not acceptable branching:

- independent actions
- more than one MIE and AO

Key Event Relationships



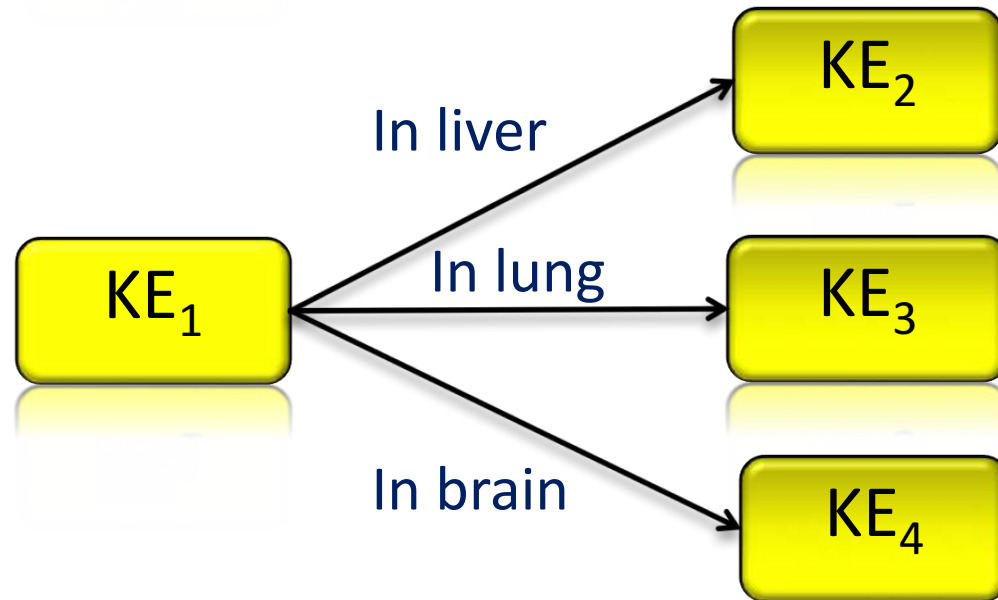
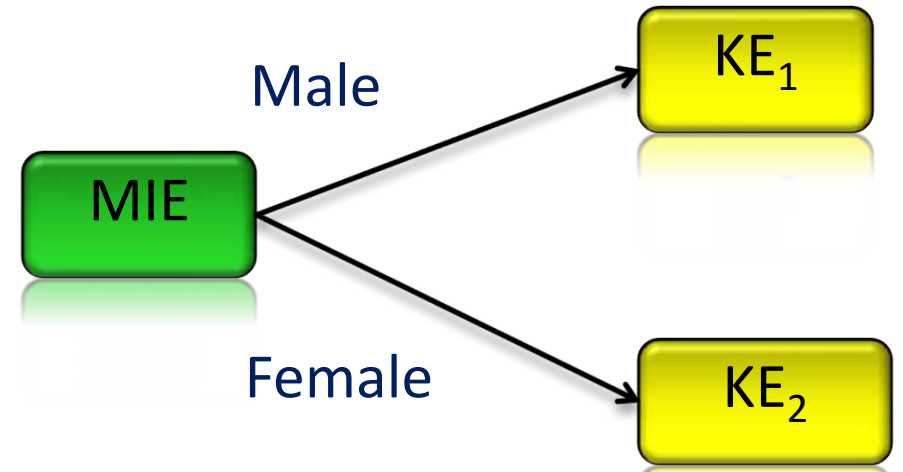
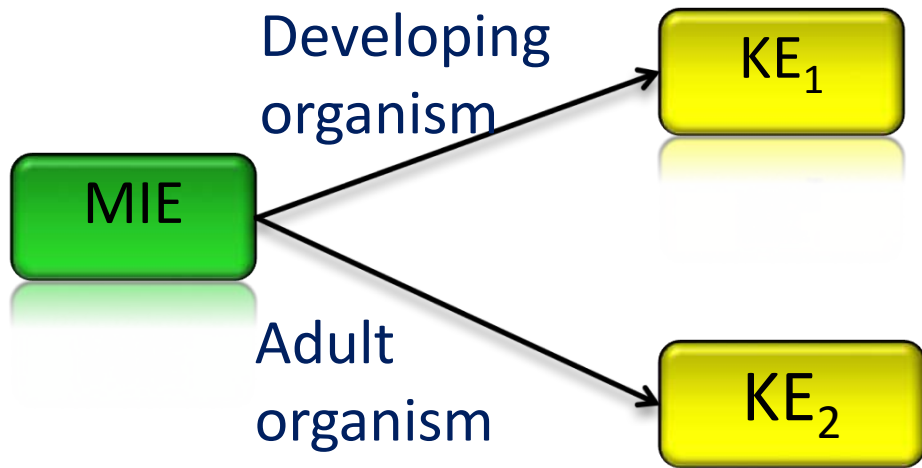
Key Event Relationship
a directed relationship

Functional unit of inference/extrapolation

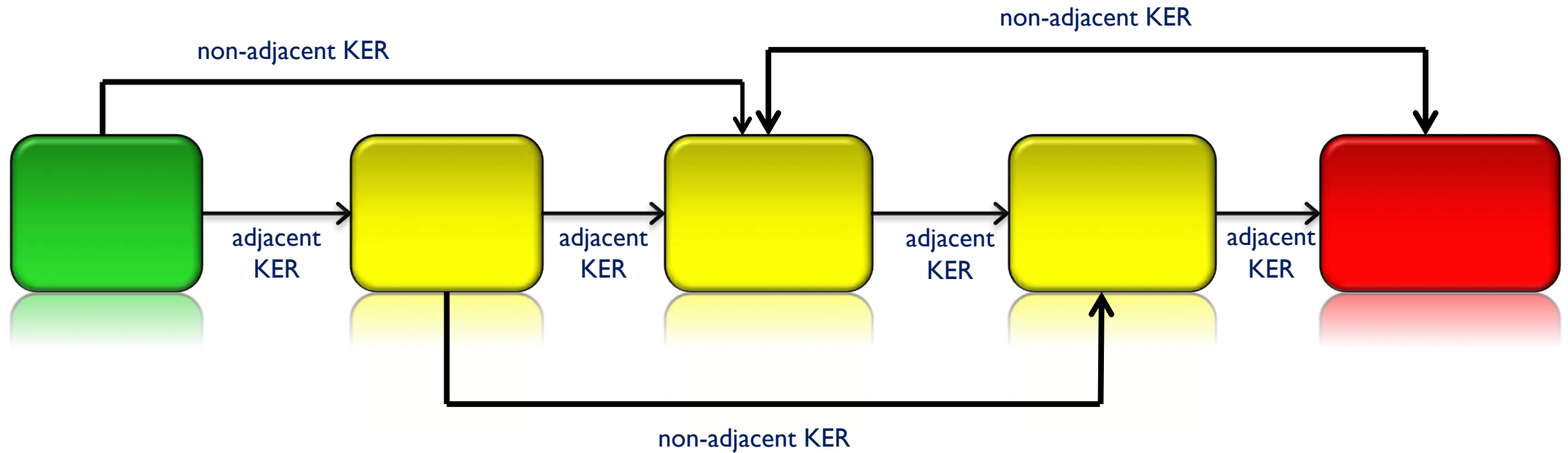
- Description
- Biological plausibility
- Empirical support
- Taxonomic applicability
- Quantitative understanding

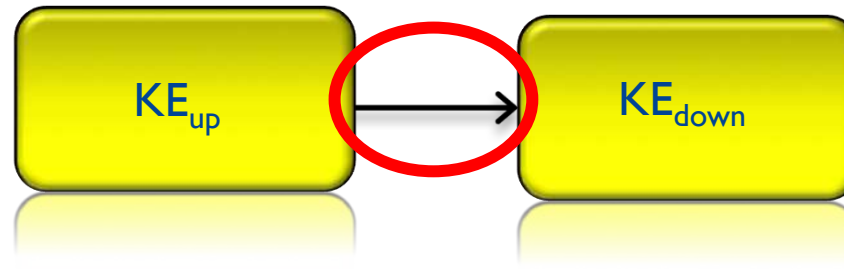
inconsistencies and uncertainties





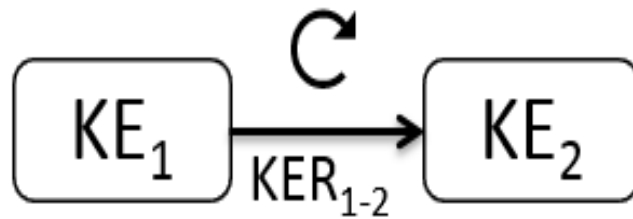
Adjacent/non-adjacent KERs



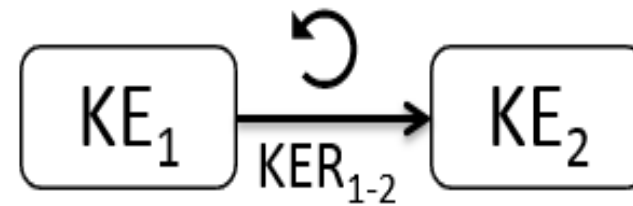


Quantitative Understanding of KERs

A.



B.

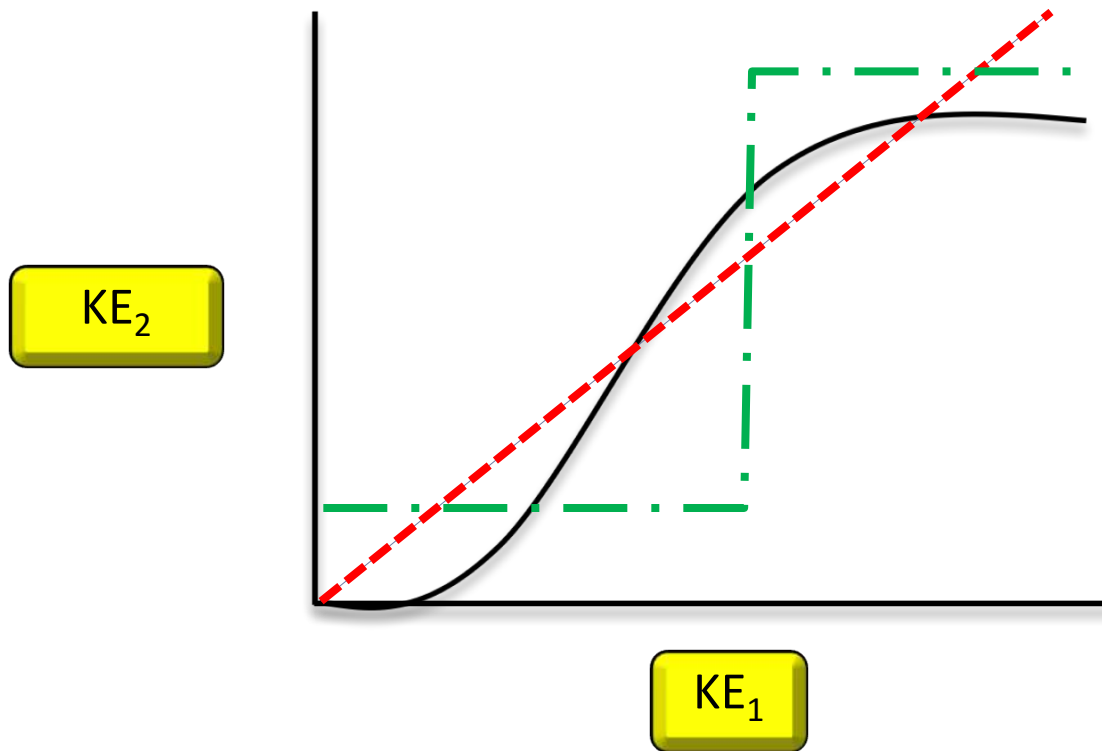


- Known feedback/feedforward loops influencing KER



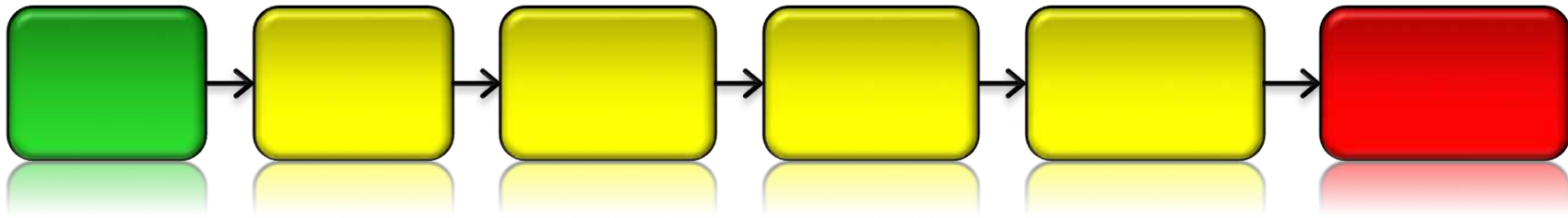
Quantitative Understanding of KERs

How much change in KE_{up} and/or for how long is needed to evoke some unit of change in KE_{down} ?

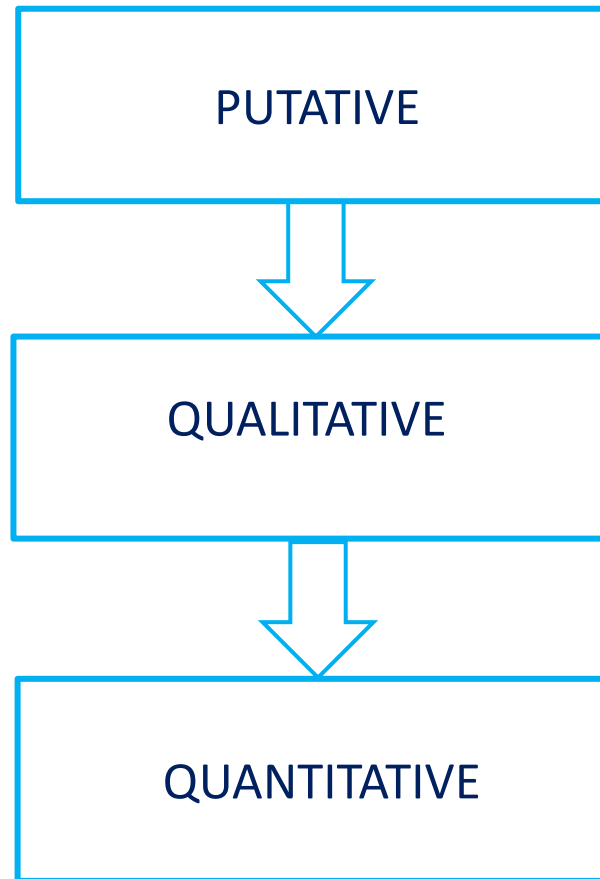


Nature of the
response-response
relationship





AOPs are living documents





A quantitative AOP is NOT EQUAL to a computer model

Quantitative KER descriptions support the development of computational models aligned with an AOP.

A qAOP model can be described as a statistical or mathematical construct that models one or more of the KERs.

The choice of the modeling method is dependent on the addressed question and the available data

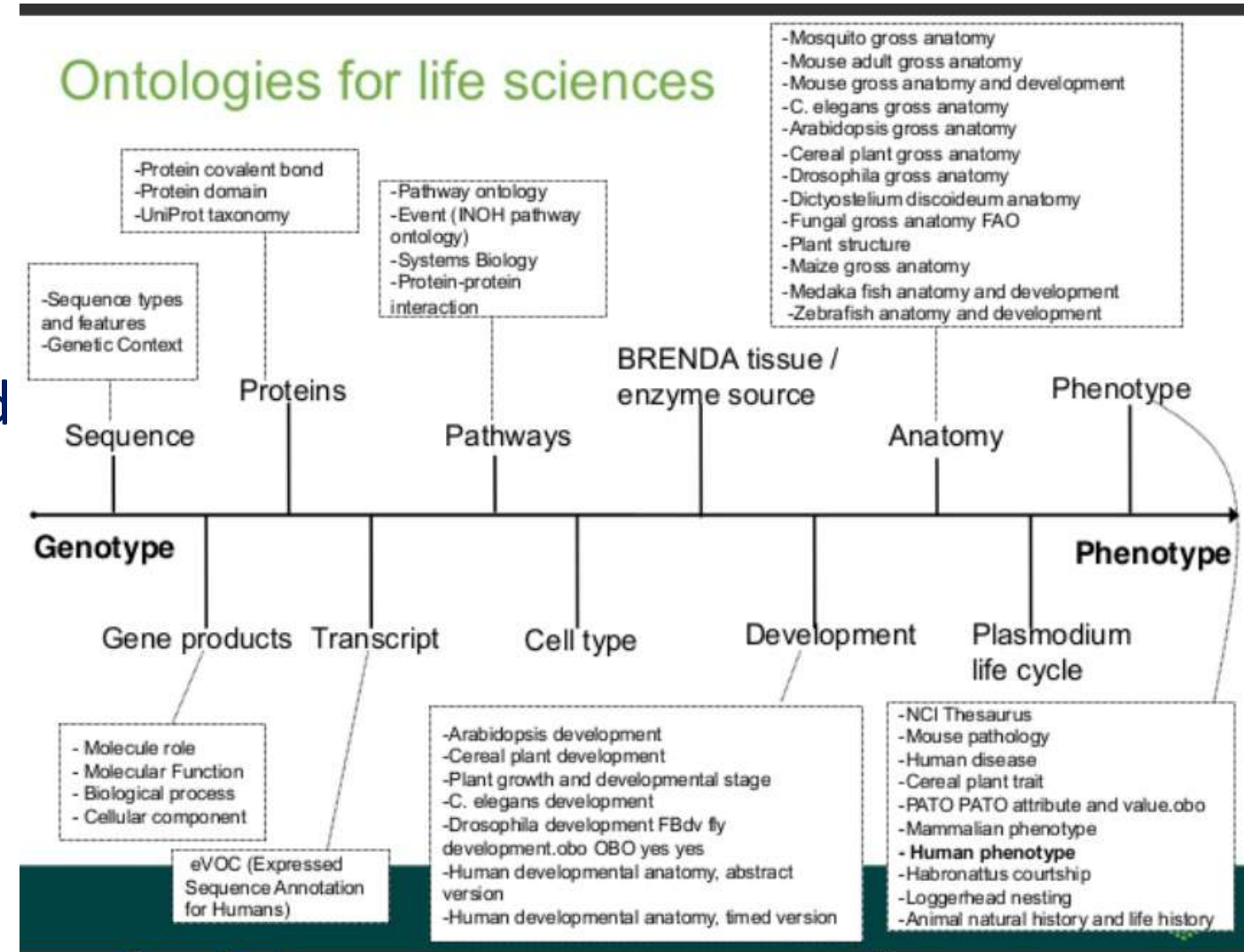




Ontologies

Ontology – a kind of controlled vocabulary of well-defined terms with specified relationships between those terms, capable of interpretation by both humans and computers.

National Center for Biomedical Ontology (NCBO)



Courtot M, EMBL-EBI,, from <https://www.slideshare.net/mcourtot/ontologies-for-life-sciences-examples-from-the-gene-ontology>

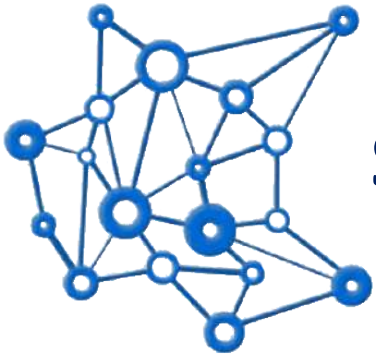
Why add ontology terms in the AOP Wiki ?



Provides more flexibility in creating new KEs.



Facilitates reuse of KEs or KERs and reduces redundancy.



Supports building of AOP networks





HOW ?

Event component(s)

KE: Molecular Initiating Event

Macro-Molecular Interactions

KER

Key Event

Cellular Responses

KER

Key Event

Organ Responses

KER

KE: Adverse Outcome

Organism Responses

KER

KE: Adverse Outcome

Population Responses

Process

Object

Action


Context
(Cell or Organ term)

Ontology terms

Event: 97

Key Event Title 

Alkylation, DNA

Short name 

Alkylation, DNA

Biological Context 

Level of Biological Organization

Molecular

Cell term 

Cell term

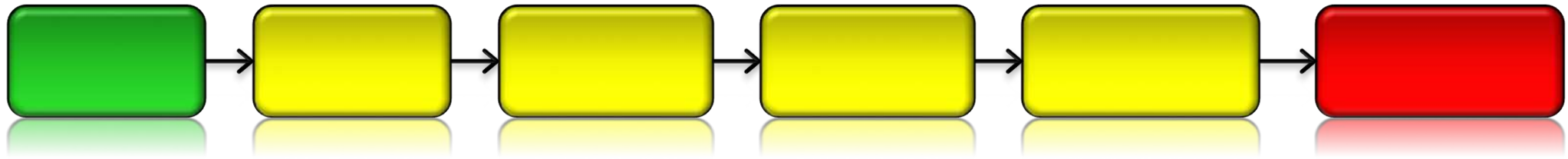
eukaryotic cell

Key Event Components 

Process	Object	Action
DNA alkylation	deoxyribonucleic acid	increased

<https://aopwiki.org/events/97>



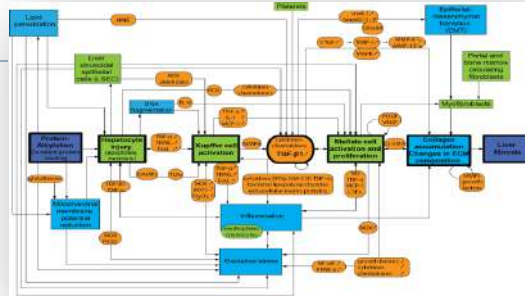


What are AOPs good for?

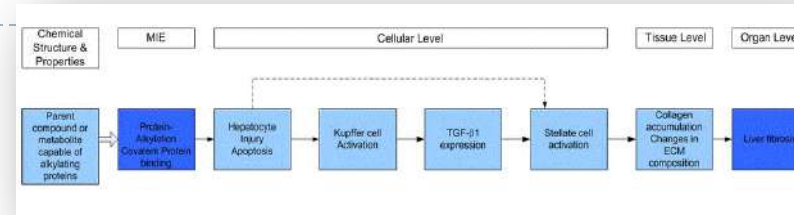


AOPs

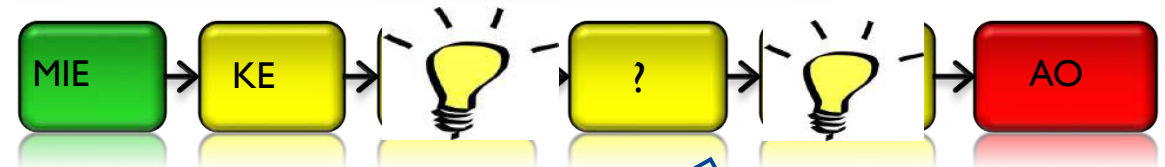
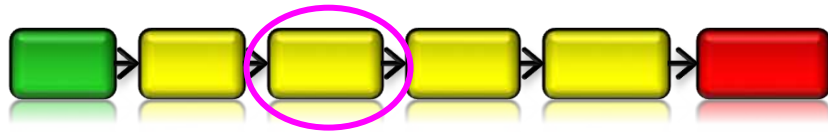
repository



clear presentation



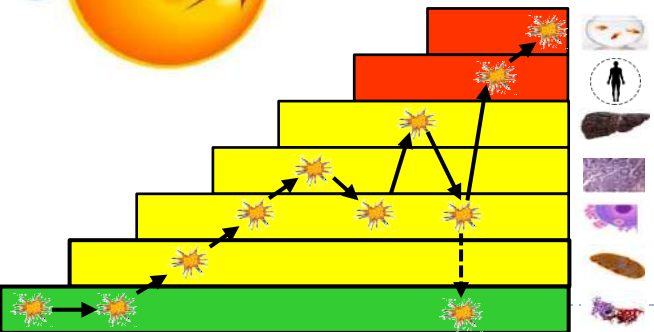
alternative tests



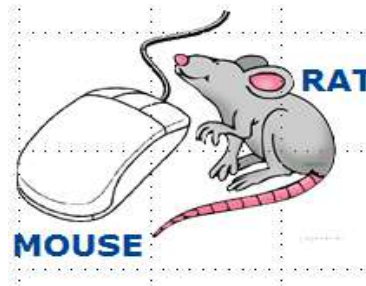
understanding



▶ biomarker



mixtures

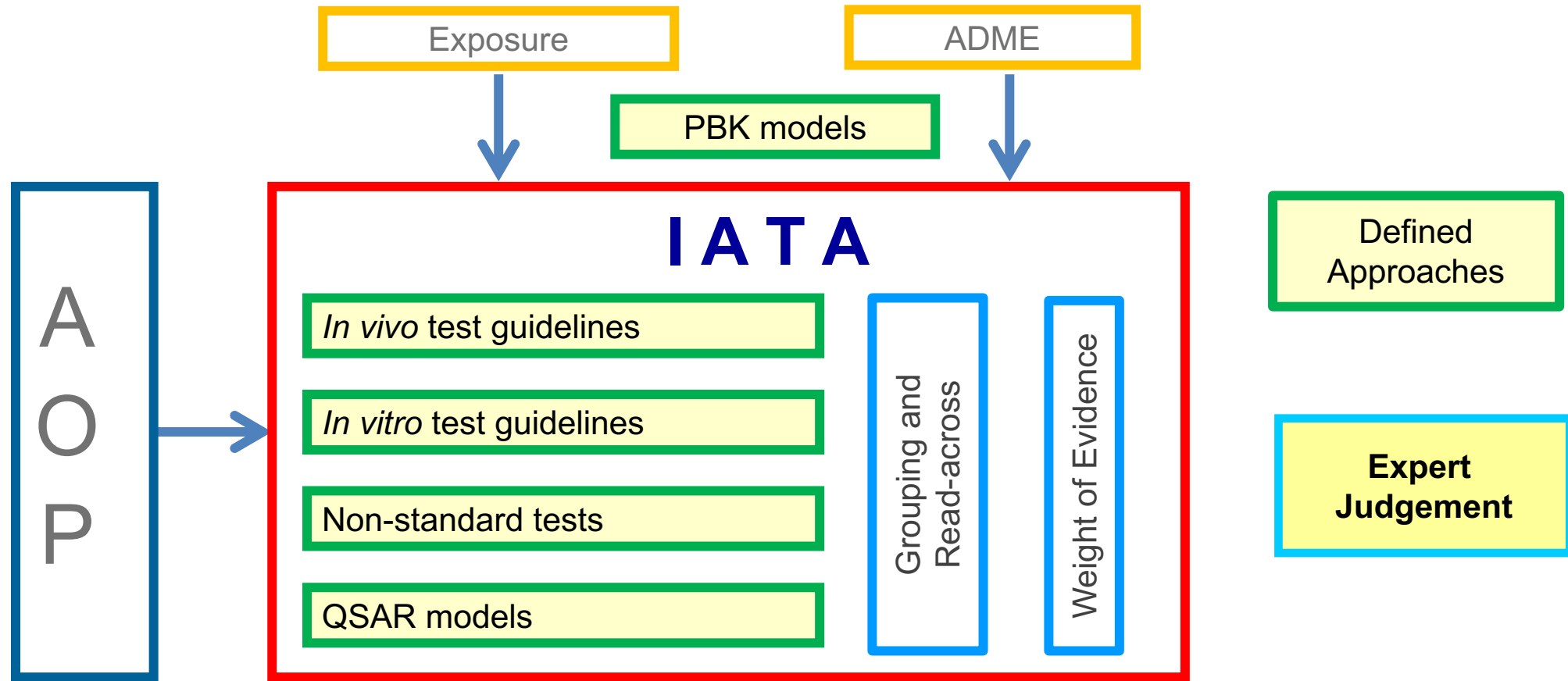


terminology



further research

AOPs in regulatory context



Every AOP is useful

KEY

AOPs are living documents for
collaboration and managing
collective knowledge

Integration of various types
of information is necessary
for risk assessment

MESSAGES

THANK YOU
for your attention !

Stay in touch



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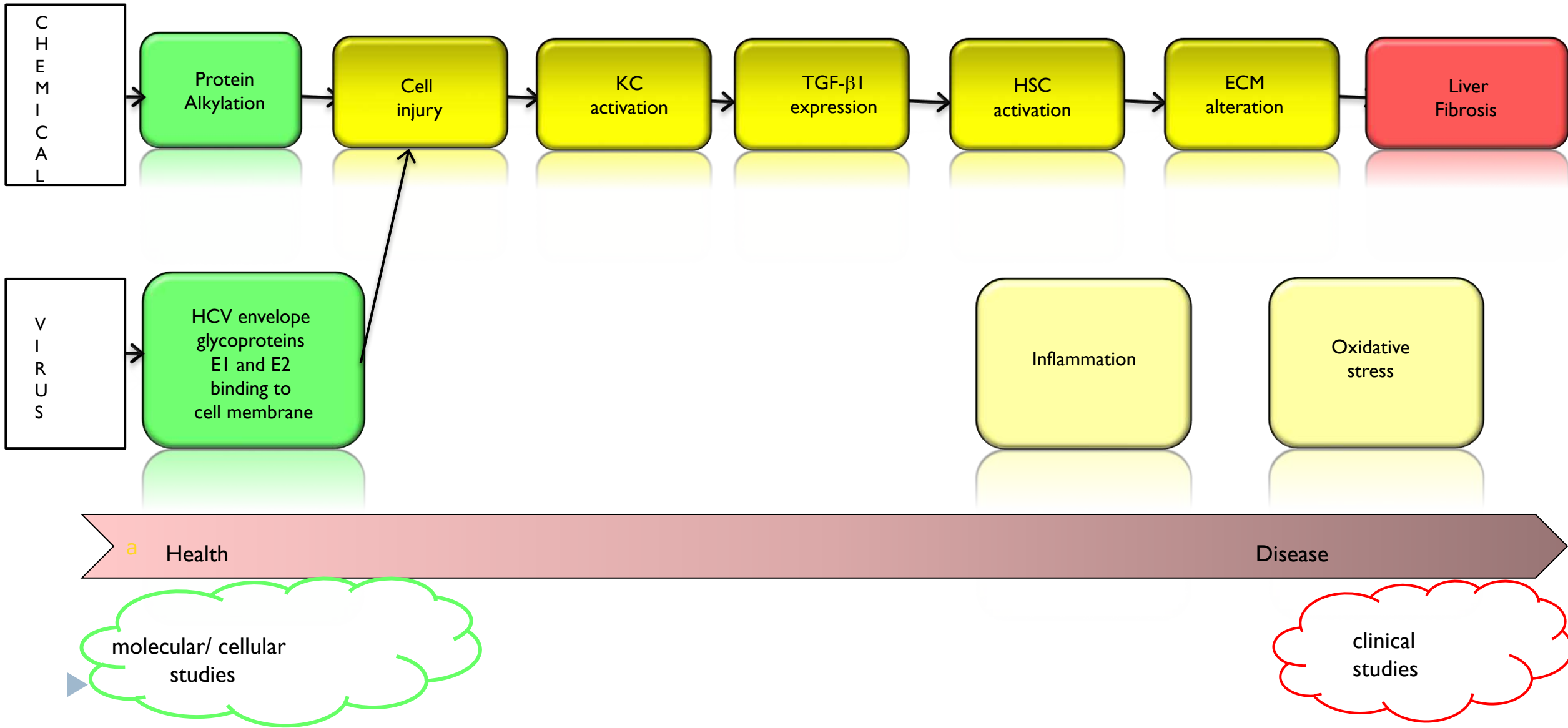
YouTube: JRC Audiovisuals

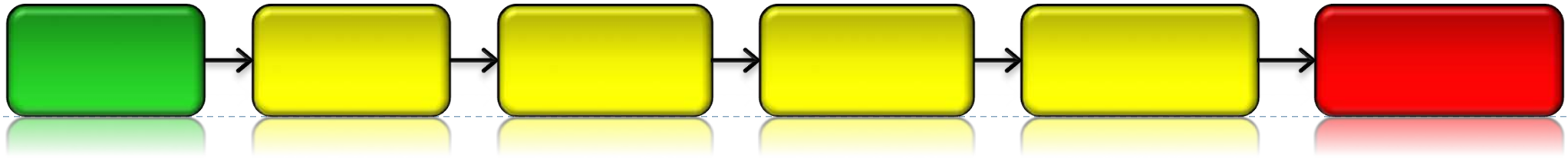


Vimeo: Science@EC

pathways to disease

AOP to Liver Fibrosis

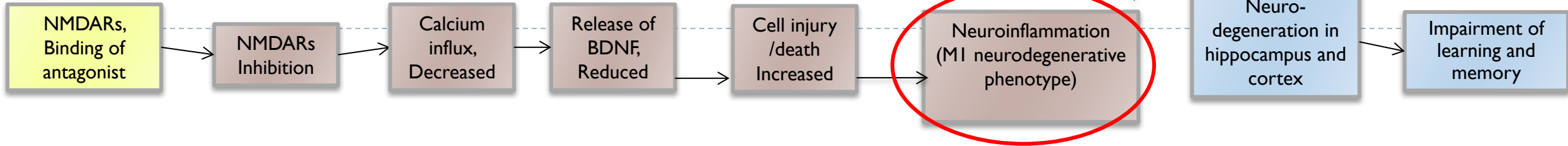




**How to represent
inflammation in AOPs
to facilitate network-building ?**



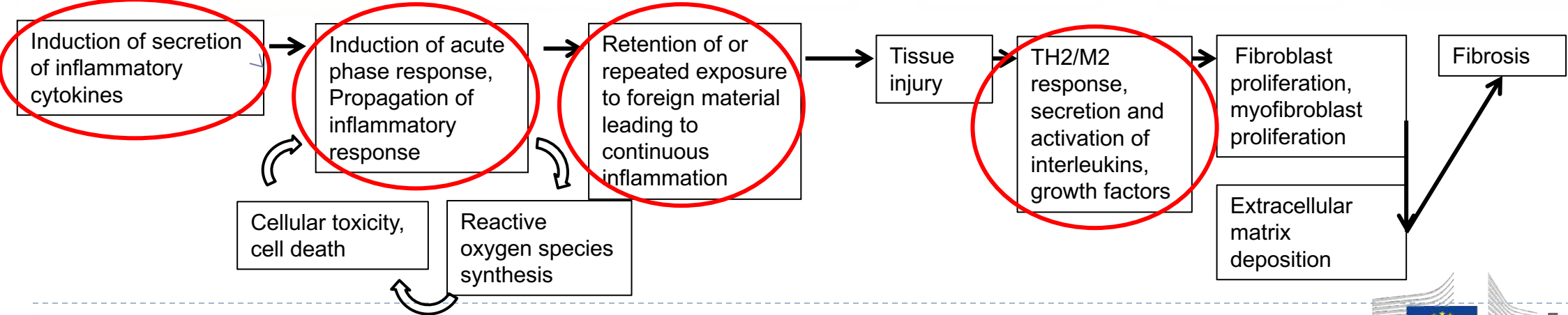
AOP 13: Chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development leads to neurodegeneration with impairment in learning and memory in aging



AOP 38 protein alkylation leading to liver fibrosis



AOP 173 resident cell activation leading to lung fibrosis



Inflammation

Upstream
Damage
Signals

Stressor-
dependent

Tissue Resident cell
activation

Increased Pro-
inflammatory
Mediators

Leukocyte
recruitment/
activation

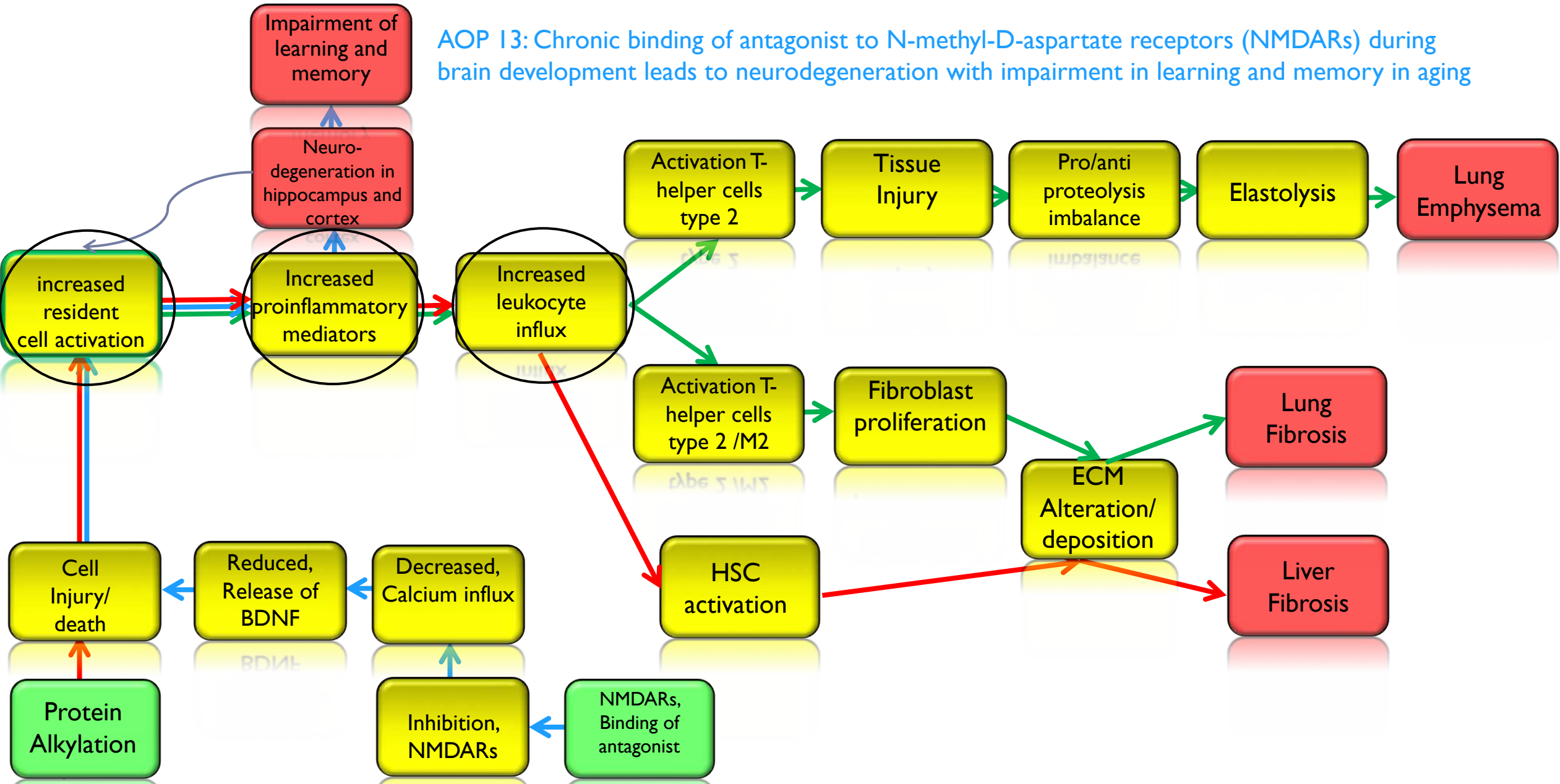
Downstream
Damage

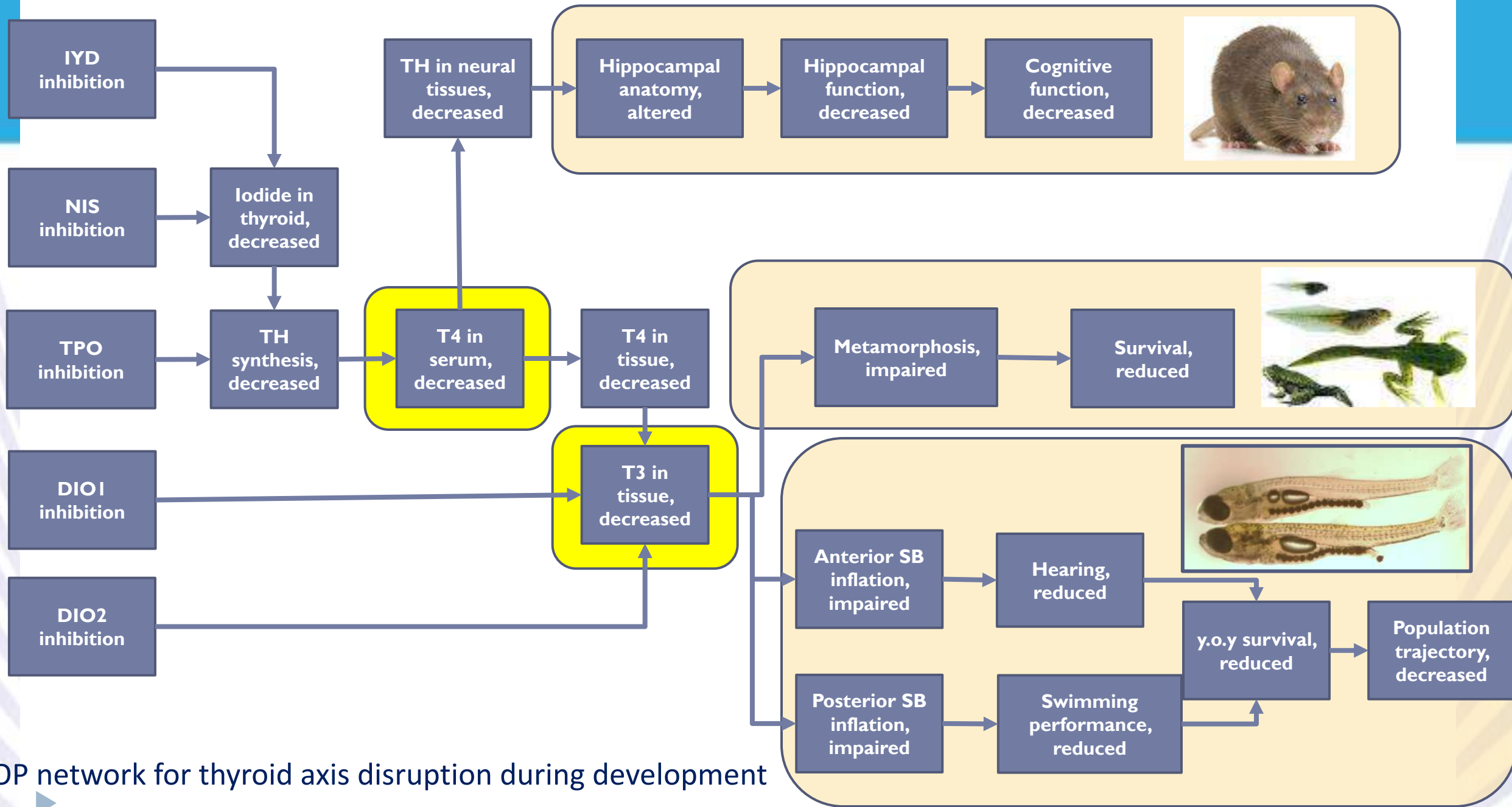
Tissue and
Context-
dependent

AOP 173 resident cell activation leading to lung fibrosis
AOP 1.25 resident cell activation leading to lung emphysema

AOP 38 protein alkylation leading to liver fibrosis

AOP 13: Chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development leads to neurodegeneration with impairment in learning and memory in aging



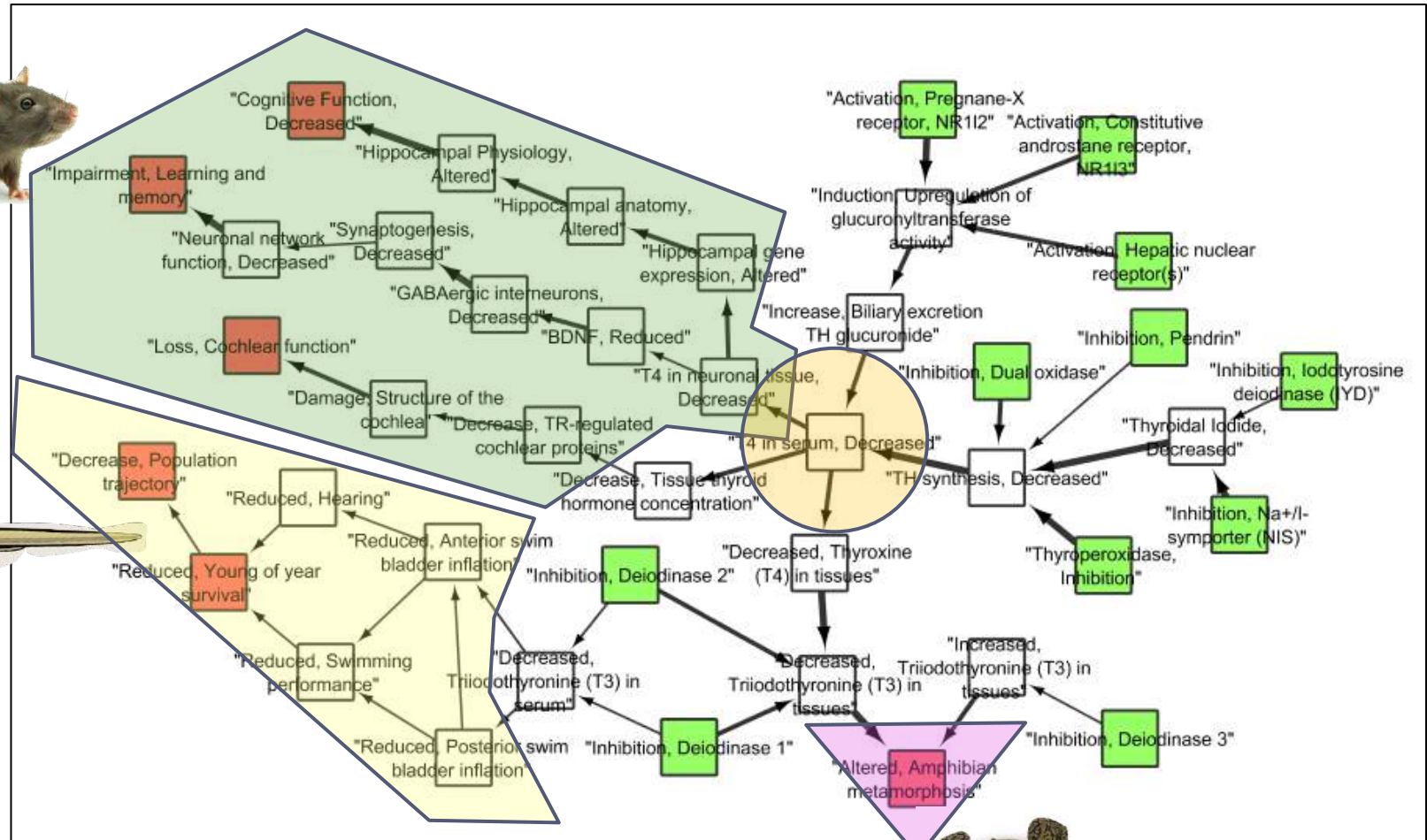


AOP network for thyroid axis disruption during development

Network of 14 AOPs
Decreased serum T4

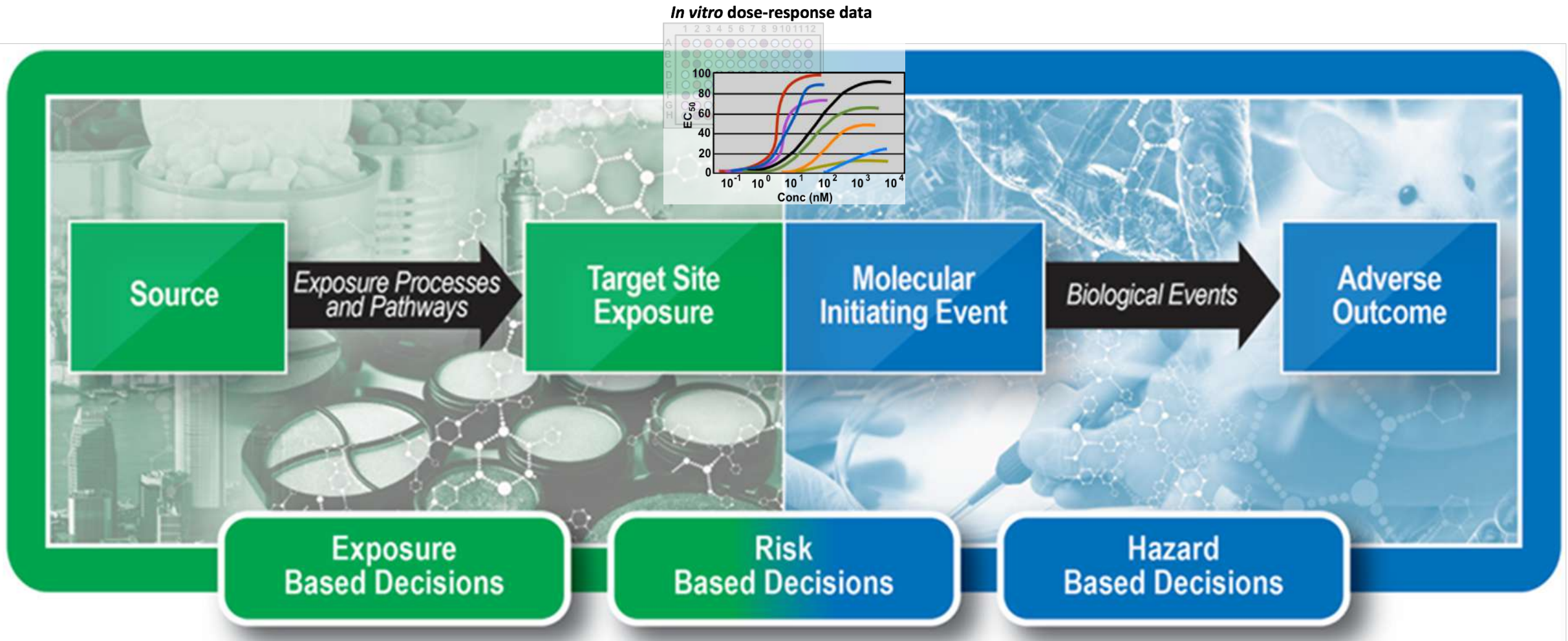


Adverse outcomes in vertebrate development



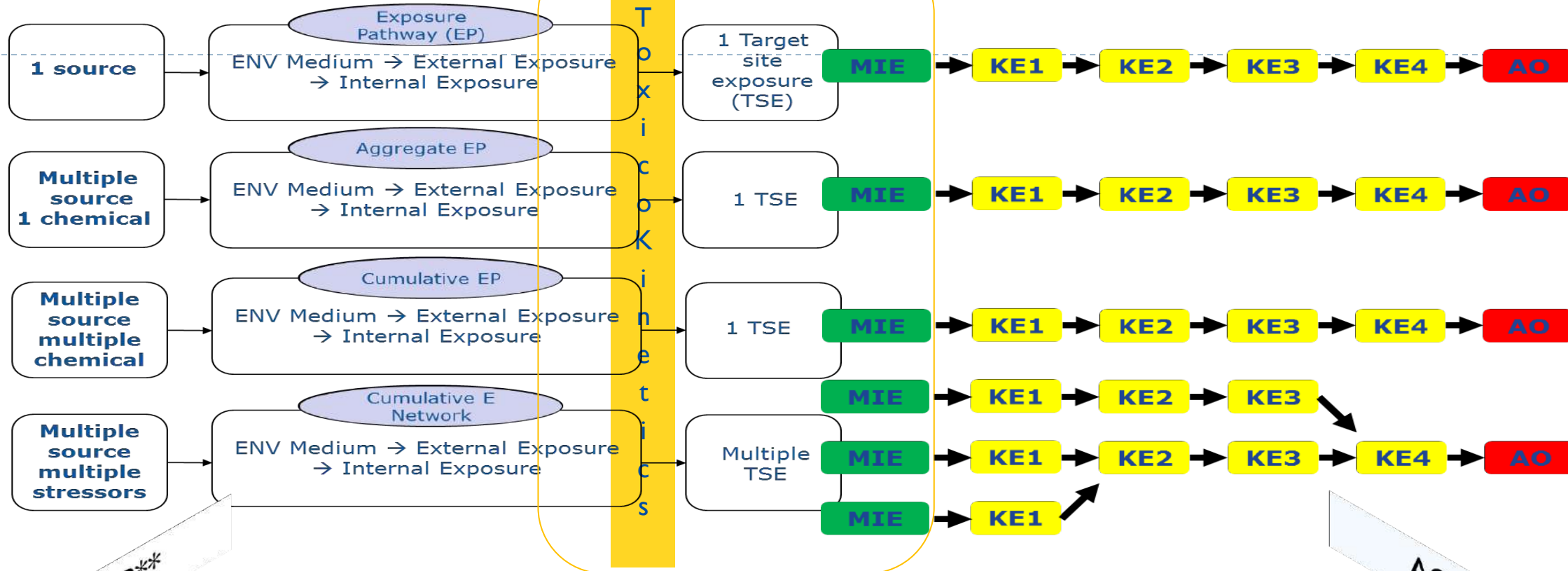
Aggregate Exposure Pathway (AEP)

A flexible, data-driven framework to organize exposure data for supporting exposure based decision making, prediction, and risk assessment

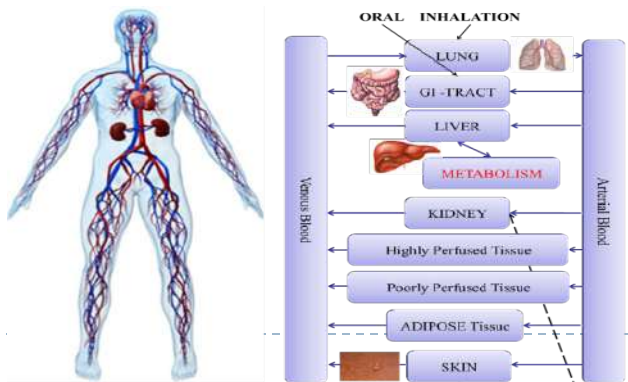
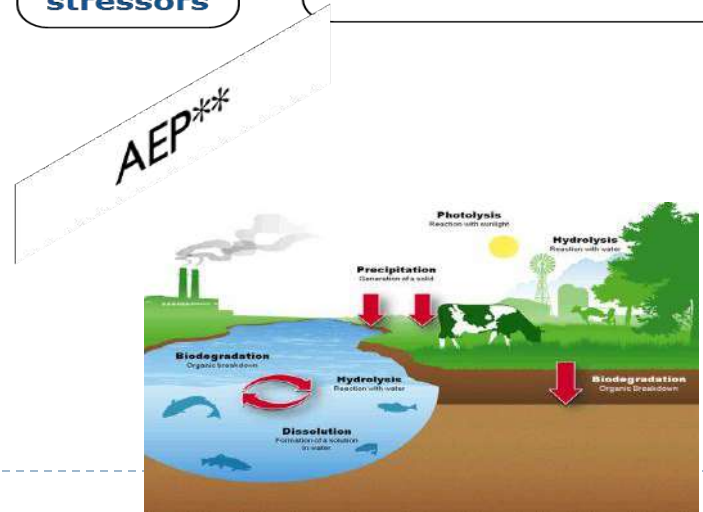


Aggregate Exposure Pathway

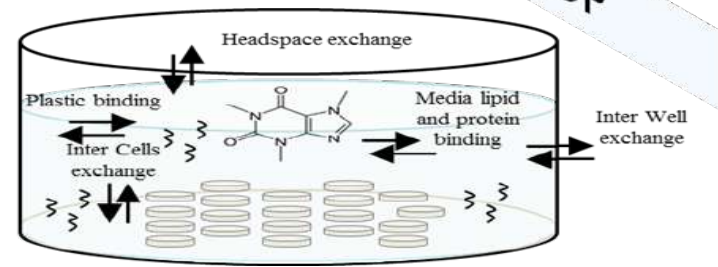
Adverse Outcome Pathway



Toxicodynamics

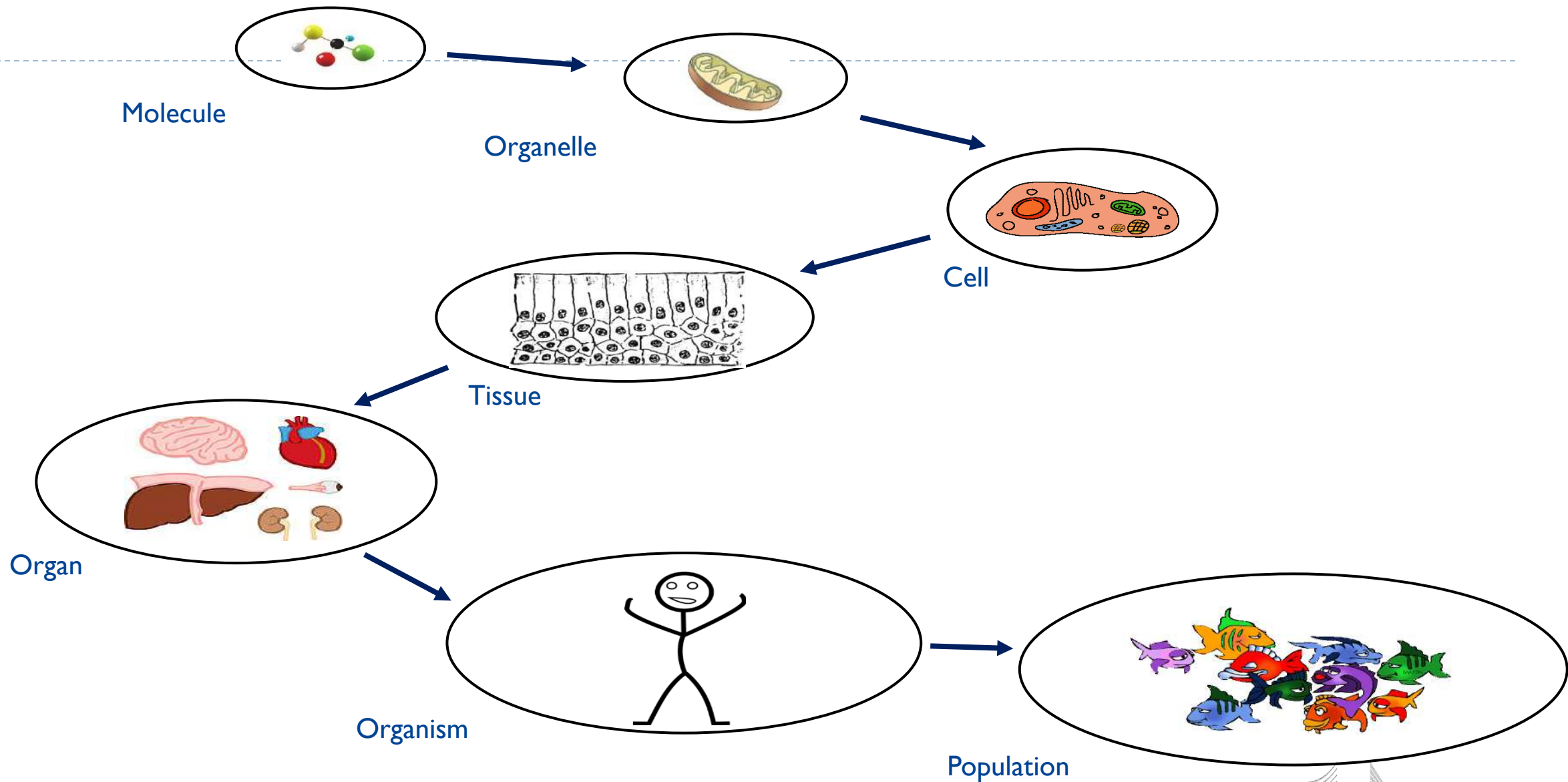


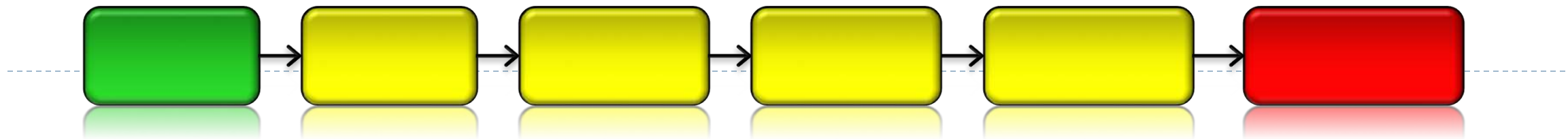
PBK modeling



AOP

Levels of biological organisation



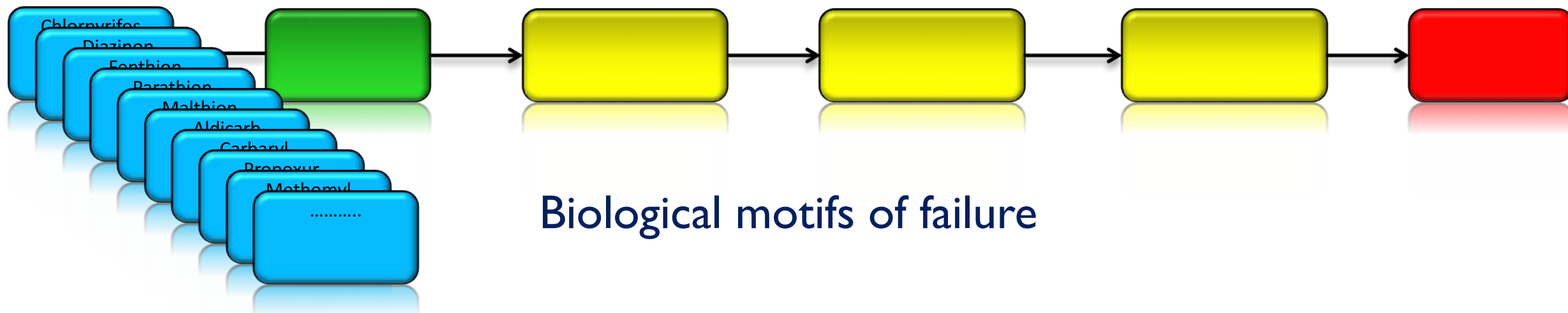


Principles of AOP development



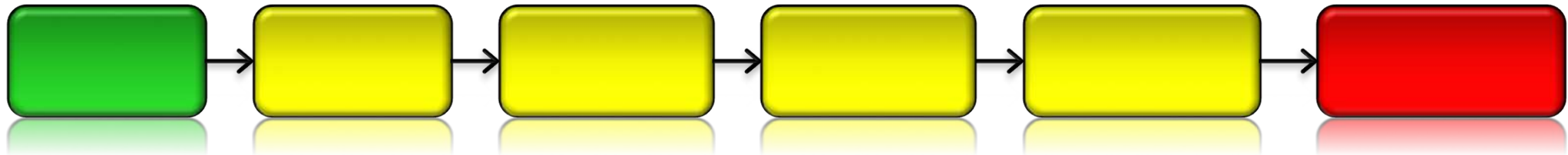


AOPs are NOT chemical-specific





AOPs are MODULAR KEs

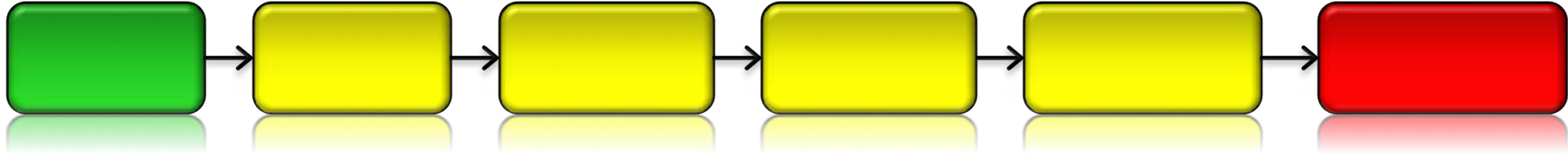


- measurable
- essential

Functional unit of observation/verification

- Description
- Methods for observing/measuring
- Taxonomic applicability

Two specialised KEs



Molecular initiating event (MIE)

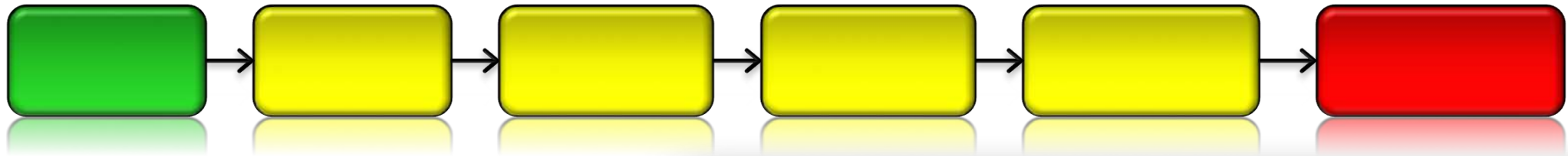


Adverse Outcome (AO)

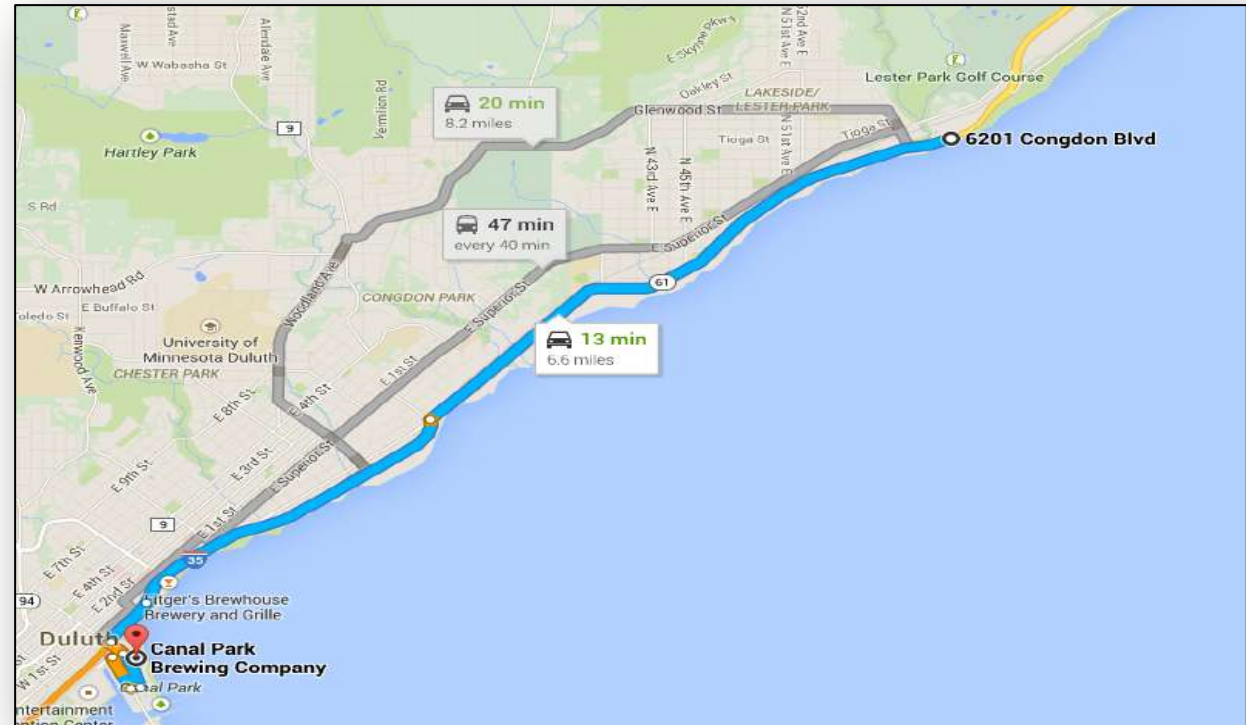




AOPs are a pragmatic functional unit of development and evaluation



Linear, no branches





AOP networks are the functional unit of prediction

Key events shared by multiple AOPs

KERs shared by multiple AOPs

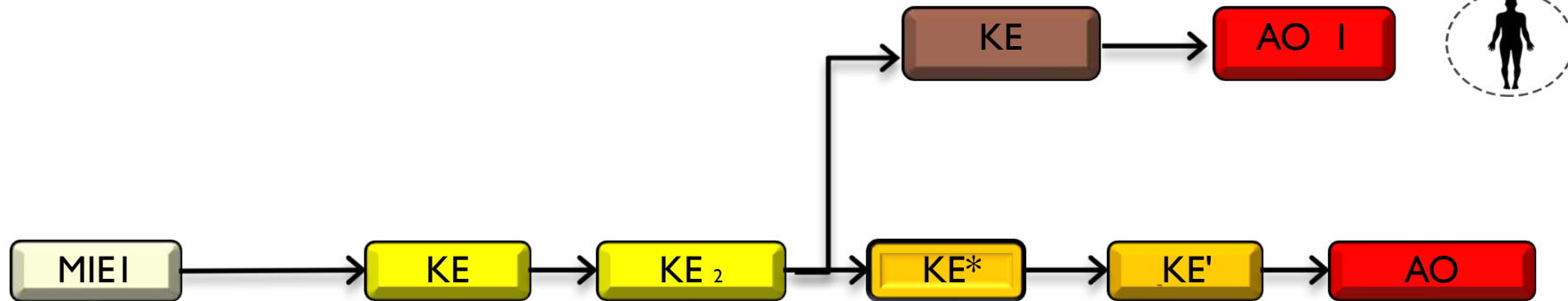
AOP 1



AOP 2



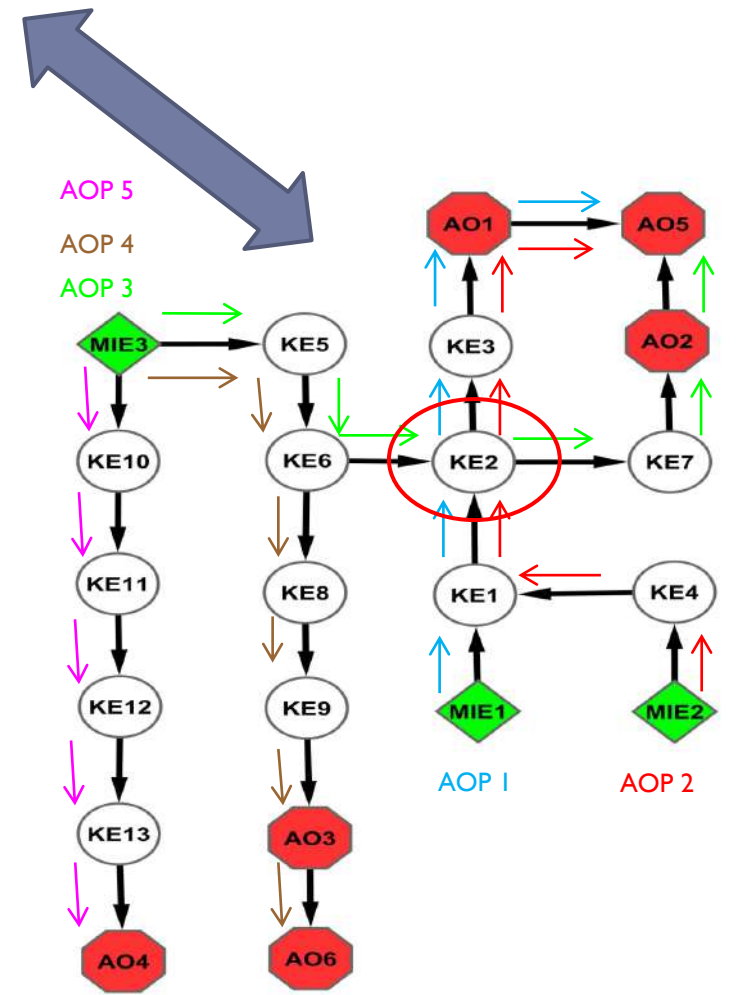
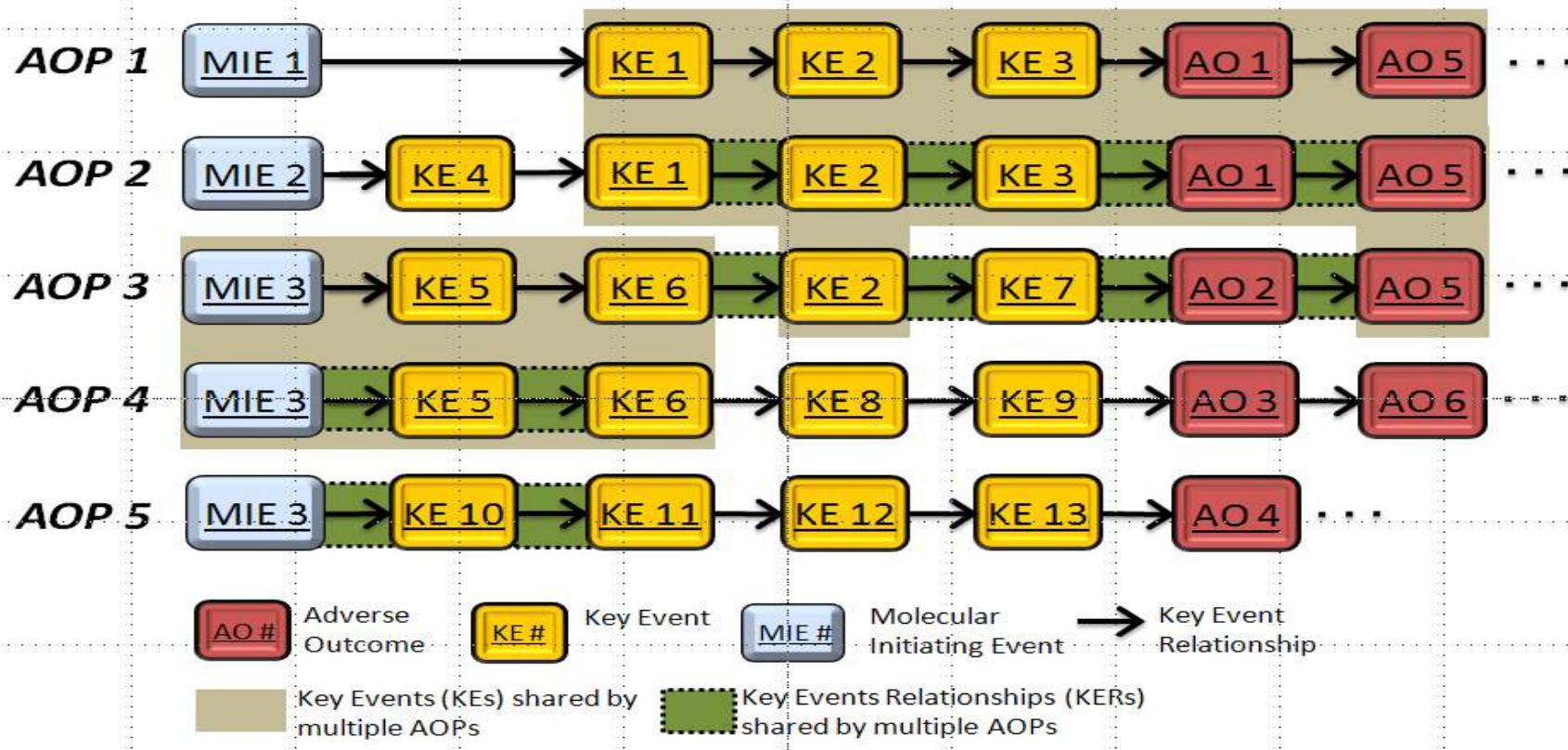
AOP 1

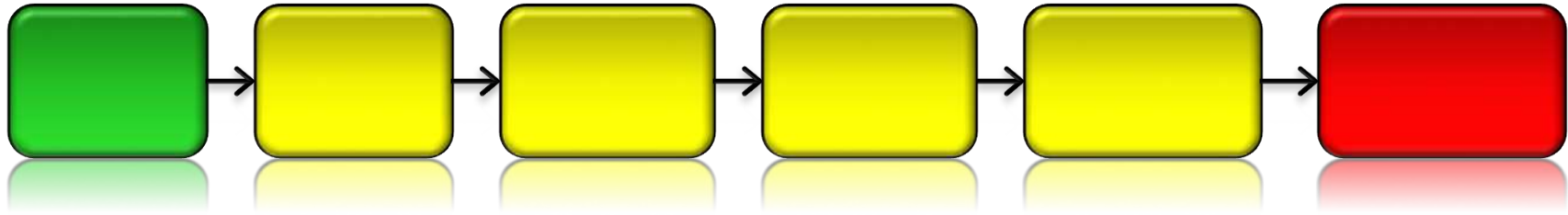


AOP 2



AOP networks





AOPs are living documents

AOPs are a way of organizing existing knowledge

There is no objective “complete AOP”

