Maurice WHELAN

European Commission

The Joint Research Centre (JRC)

As the science and knowledge service of the Commission our mission is to support EU policies with independent evidence throughout the whole policy cycle.

~ 3000 staff

Almost 75% are scientists.

Headquarters in Brussels.

Research facilities located in 5 Member States.

European Commission

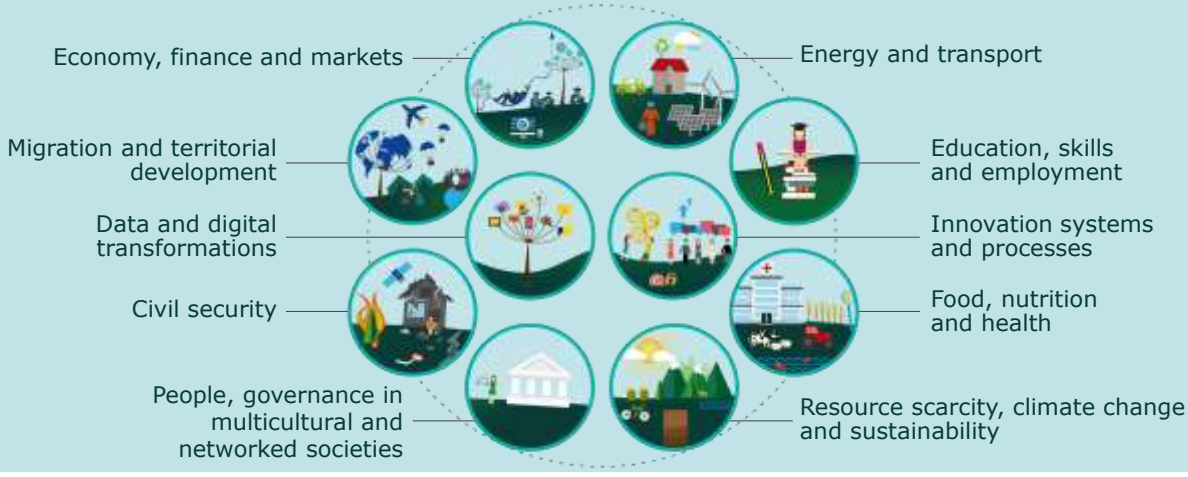
JRC sites

Headquarters in Brussels and research facilities located in **5 Member States:**

- Belgium (Geel)
- Germany (Karlsruhe)
- Italy (Ispra)
- The Netherlands (Petten)
- Spain (Seville)

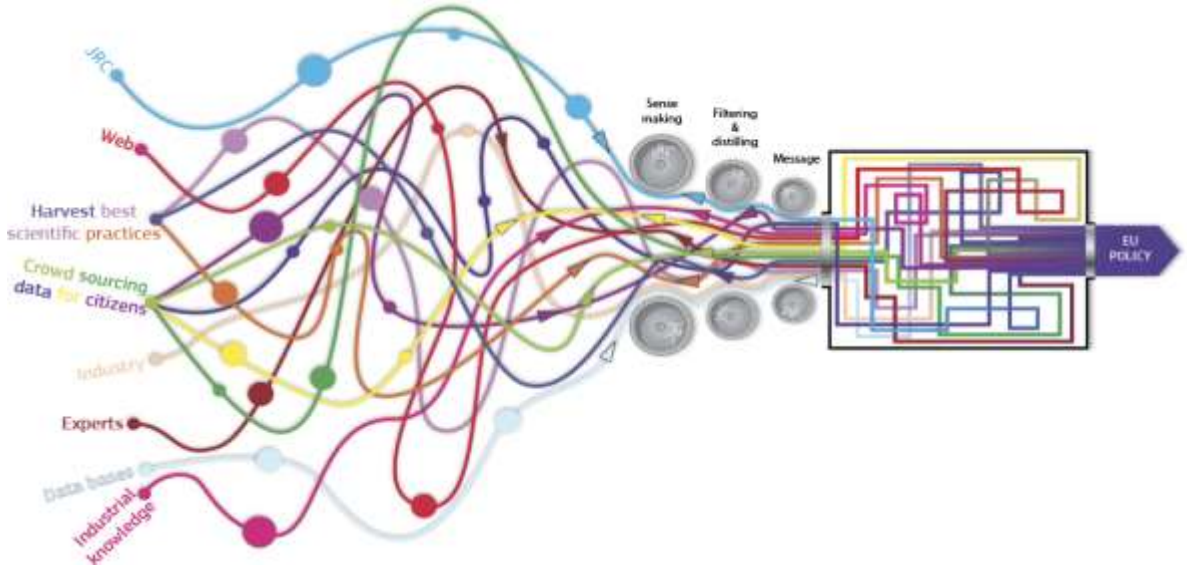
European Commission

JRC 10 Priority Nexus



European Commission

Making scientific evidence available for EU policy



The European Union Reference Laboratory for Alternatives to Animal Testing

- **Research**
- **Validation**
- **Dissemination**
- **Promotion**

EURL ECVAM

EURL ECVAM
Alternatives to Animal Testing
1991 - 2016

European Commission

EURL ECVAM Annual Status Report

European Commission

Adverse Outcome Pathways

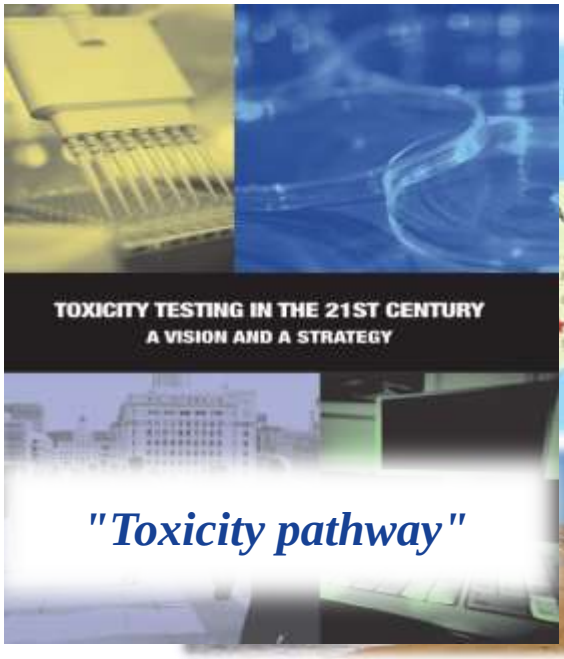
Maurice Whelan

Francqui Chair 2017-18

Vrije Universiteit Brussel

20th March 2018

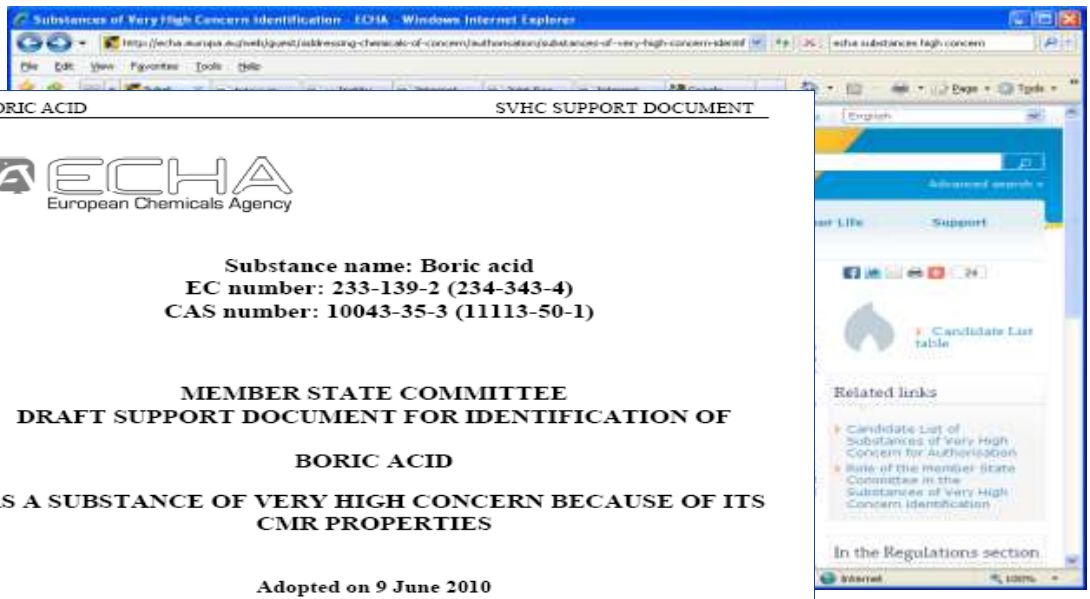
European Commission



"Toxicity pathway"

2007

European Commission



BORIC ACID SVHC SUPPORT DOCUMENT

ECHA
European Chemicals Agency

Substance name: Boric acid
EC number: 233-139-2 (234-343-4)
CAS number: 10043-35-3 (11113-50-1)

MEMBER STATE COMMITTEE
DRAFT SUPPORT DOCUMENT FOR IDENTIFICATION OF

BORIC ACID

AS A SUBSTANCE OF VERY HIGH CONCERN BECAUSE OF ITS CMR PROPERTIES

Adopted on 9 June 2010

European Commission

New technologies and tools

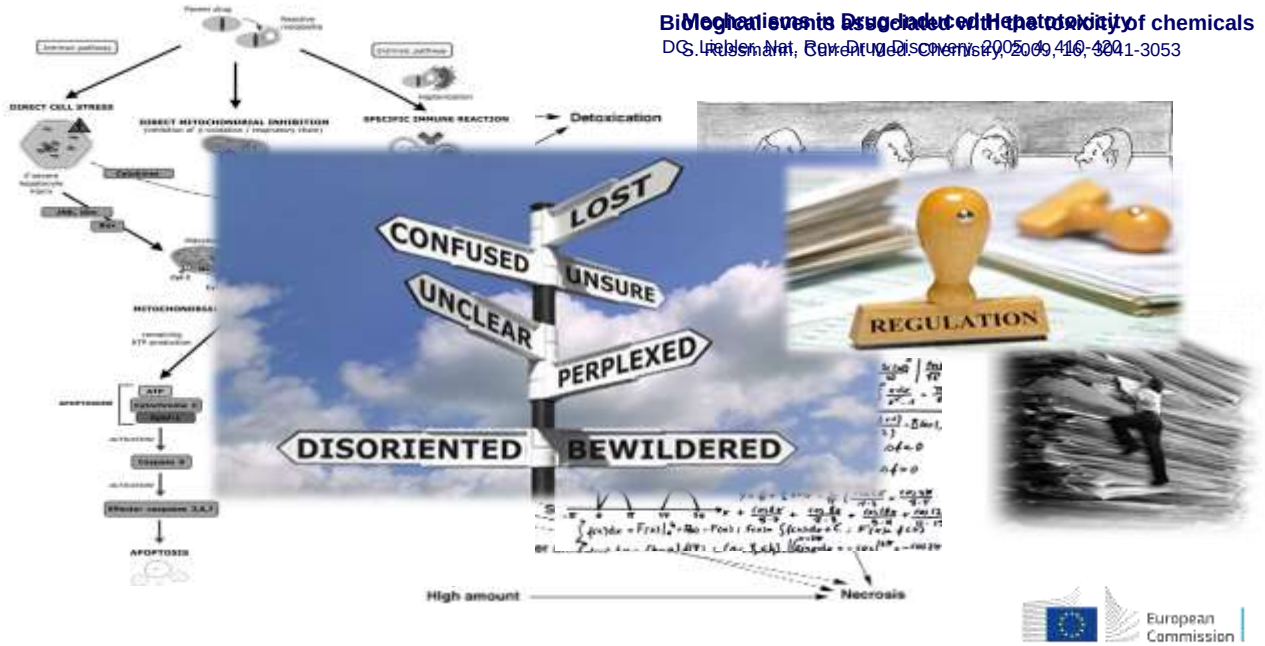
European Commission

Biological events associated with the toxicity of chemicals

Mechanisms in Drug-induced Hepatotoxicity

DG Ireijer, Nat. Rev. Drug Discovery, 2005, 4, 416-420

S. Ruebsmann, Current Med. Chemistry, 2009, 16, 3041-3053



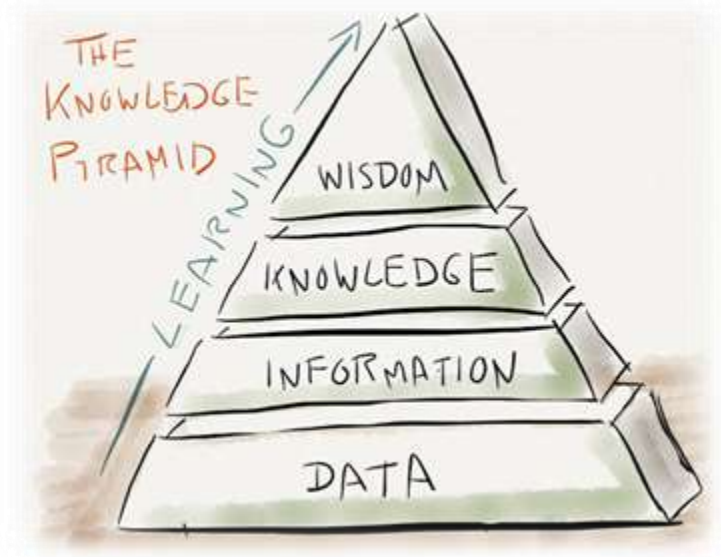
European Commission

Knowledge and understanding

"… unprecedented ability to collect data about nature but **there is now a crisis developing in biology**, … we can't talk to each other … unstructured information does not enhance understanding …"

"We need a framework to put all of this knowledge and data into … **driving toward that framework** is really the big challenge."

Sydney Brenner. Molecular Biologist and Nobel Laureate



… how to make toast …

A novel approach to manage biological and toxicological knowledge

Key Attributes

A. Carusi et al. / Science of the Total Environment 628–629 (2018) 1542–1556

European Commission

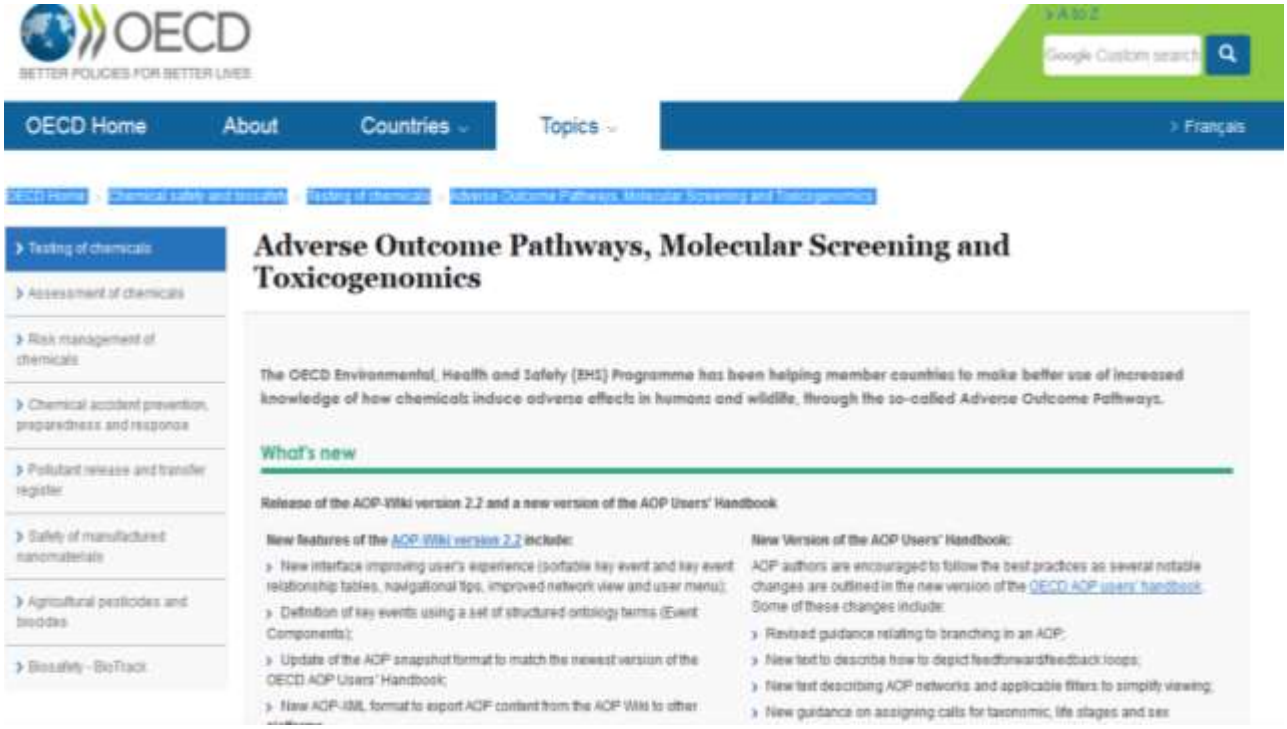
Exploiting knowledge

Stakeholder Appeal

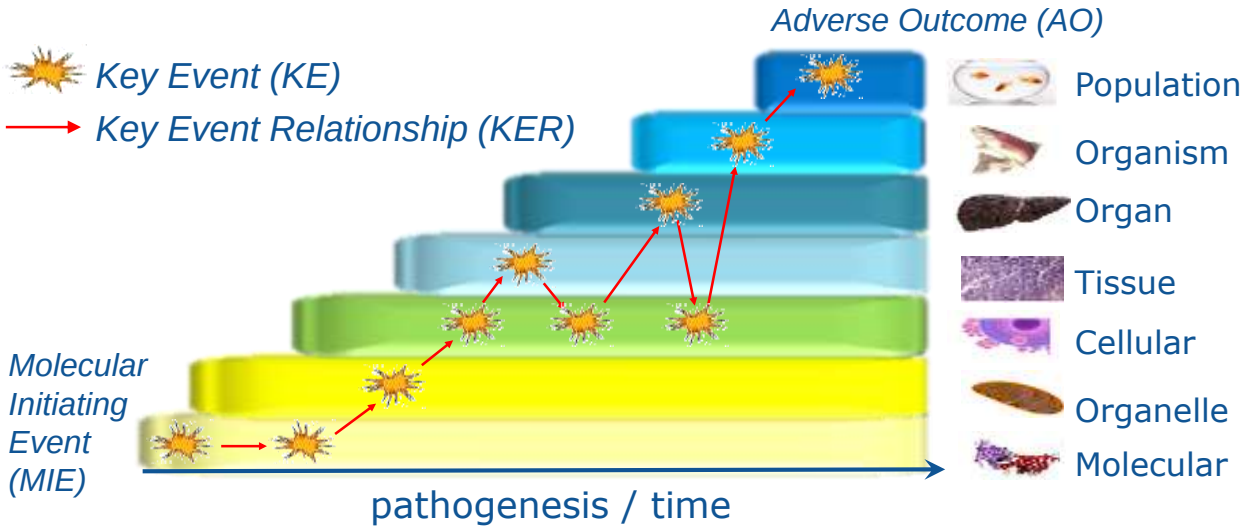
Applications

A. Carusi et al. / Science of the Total Environment 628–629 (2018) 1542–1556

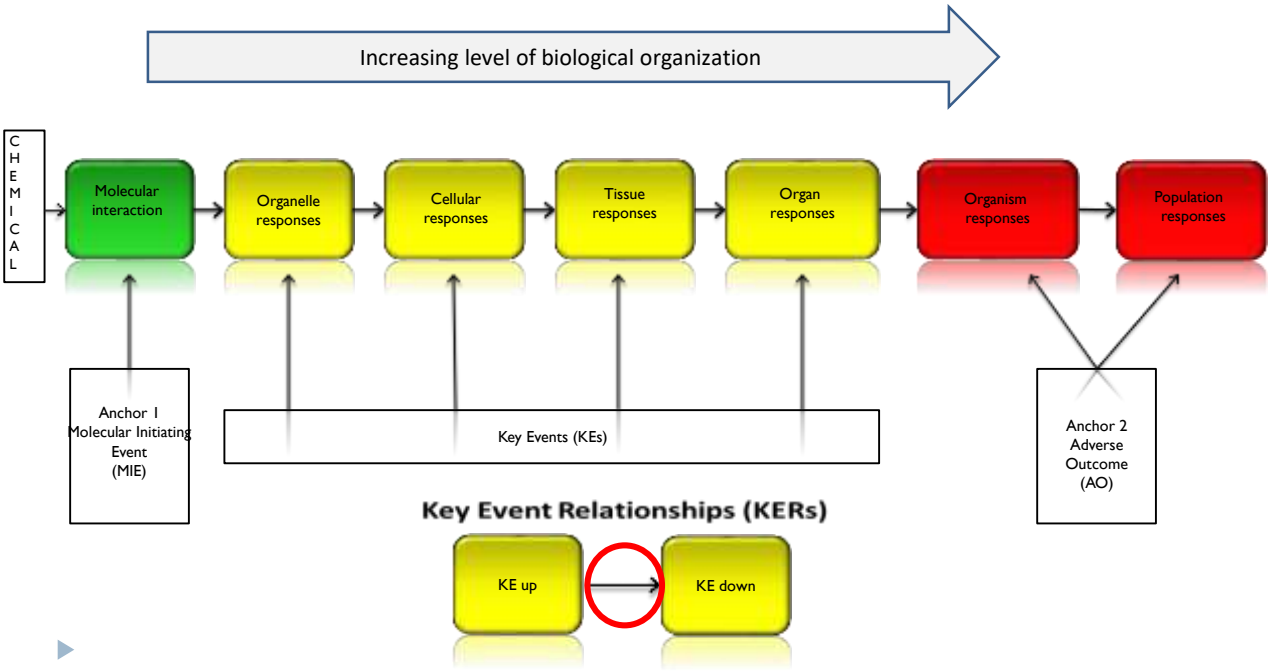
European Commission



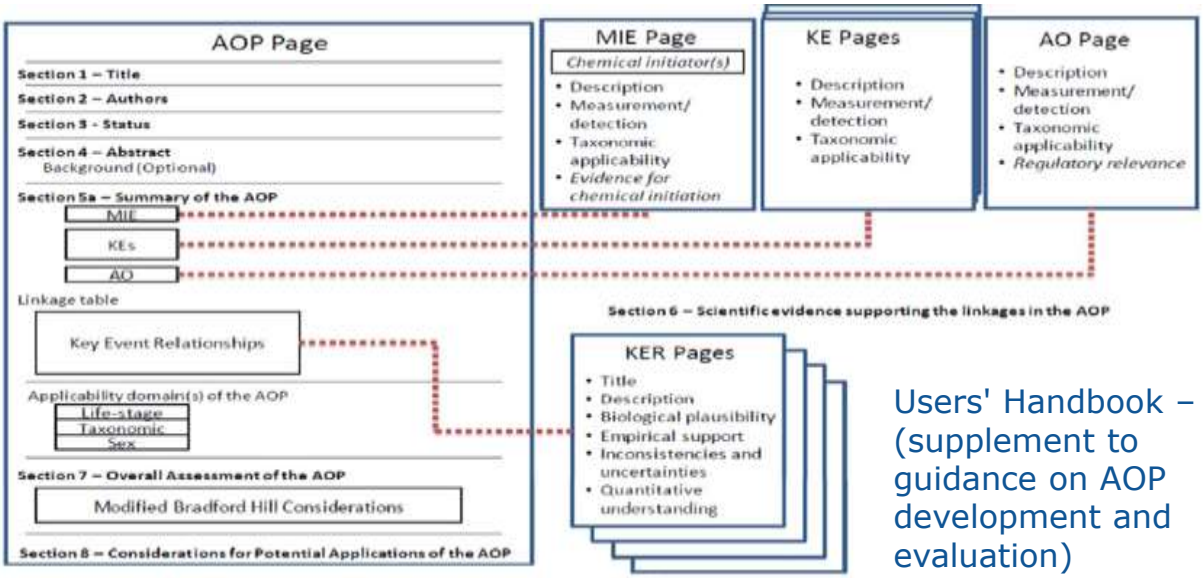
Adverse Outcome Pathways (AOP)



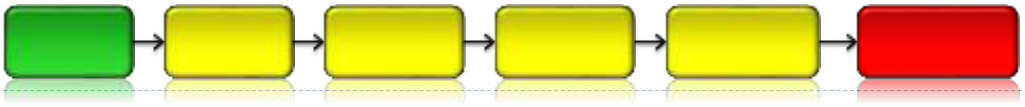
European Commission



AOP document structure

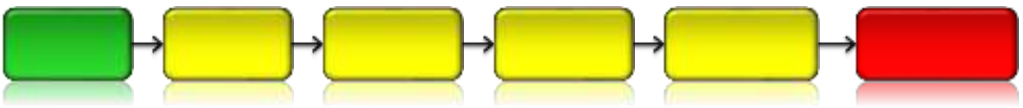


Users' Handbook – (supplement to guidance on AOP development and evaluation)



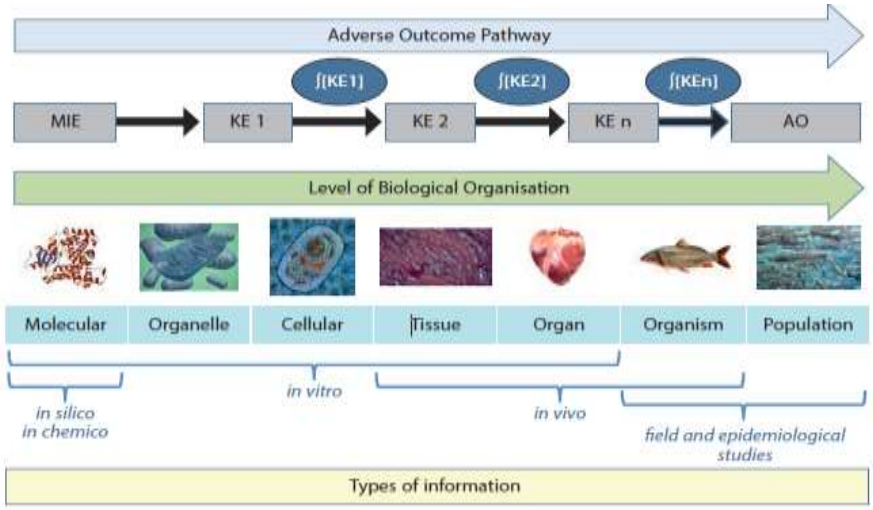
The Five Principles of AOP Development

- ❖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



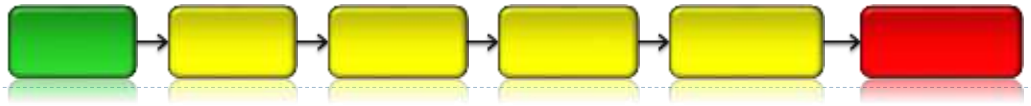
AOPs thrive because of the interactivity and multidisciplinarity of the crowd

Collection and organisation of various types of information



OECD(2017), Guidance document for the use of AOPs in developing IATA, Series on Testing & Assessment No. 260,

European Commission

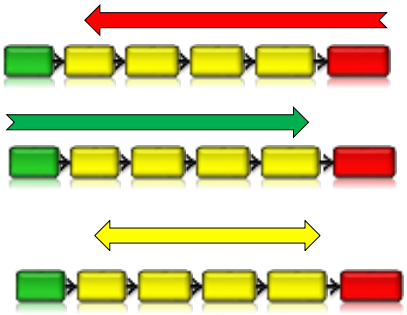


Building an AOP

European Commission

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:

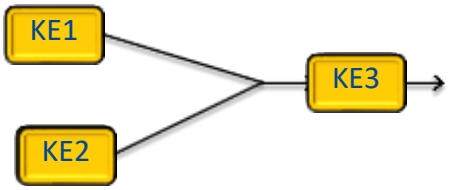
- One MIE
- Desirably, one KE at each level of biological organization
- One AO (AOPs can have more than one AO)

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

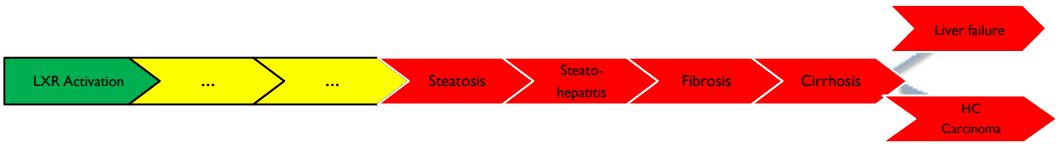
AO:

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

A.

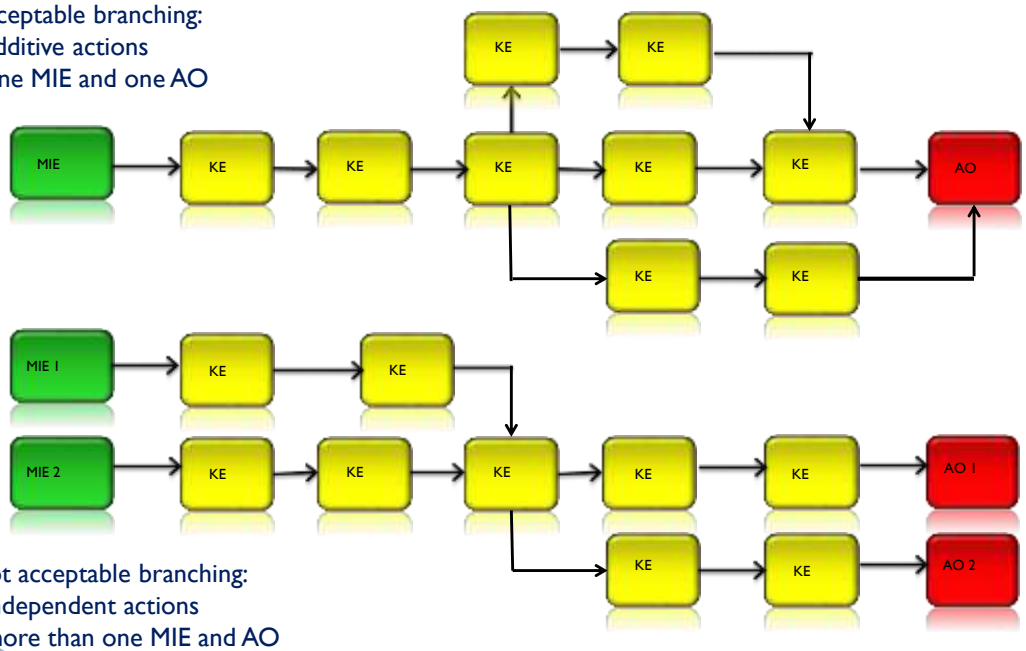
Multiple AOs in a single, sequential progression = single AOP

B.



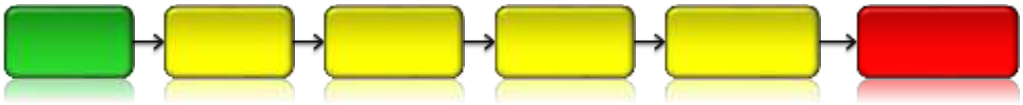
Branching = two AOPs

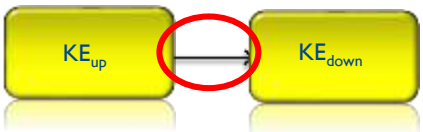
Acceptable branching:
- additive actions
- one MIE and one AO



Not acceptable branching:
- independent actions
- more than one MIE and AO

Key Event Relationships





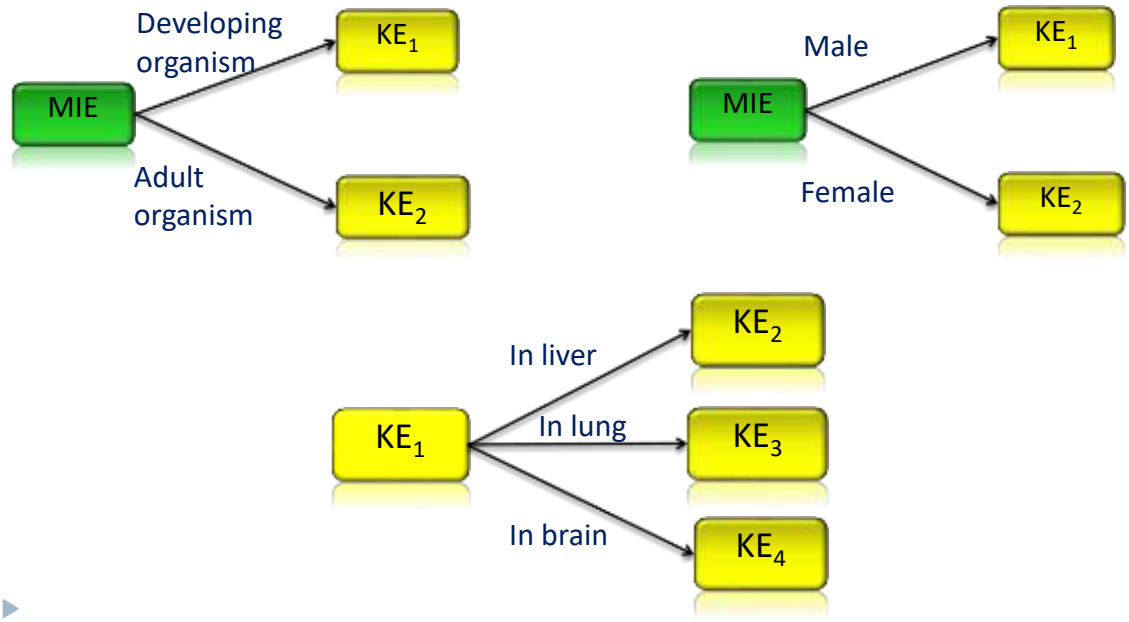
Key Event Relationship

a directed relationship

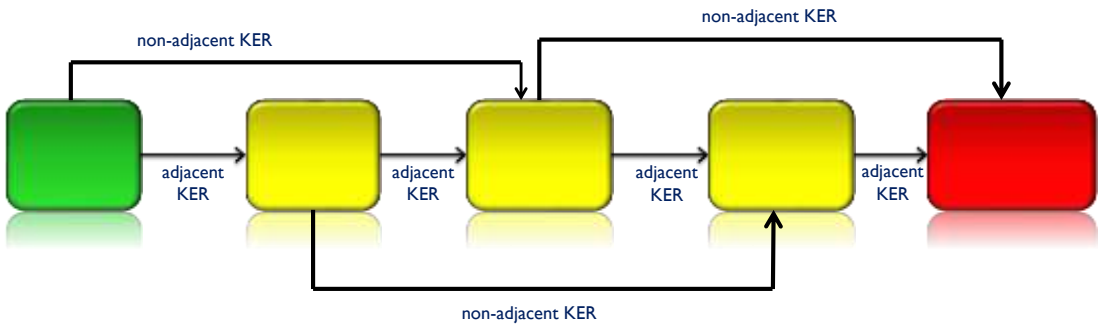
Functional unit of inference/extrapolation

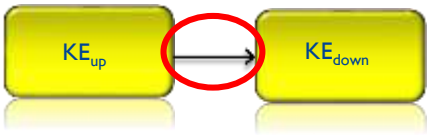
- Description
- Biological plausibility
- Empirical support
- Taxonomic applicability
- Quantitative understanding

inconsistencies and uncertainties

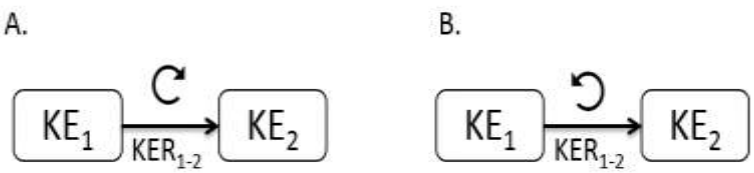


Adjacent/non -adjacent KERs





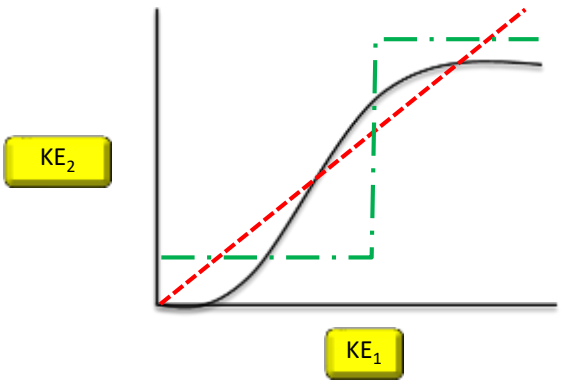
Quantitative Understanding of KERs



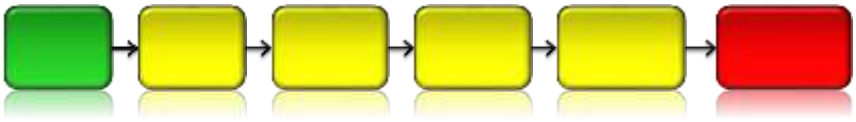
- Known feedback/feedforward loops influencing KER

Quantitative Understanding of KERs

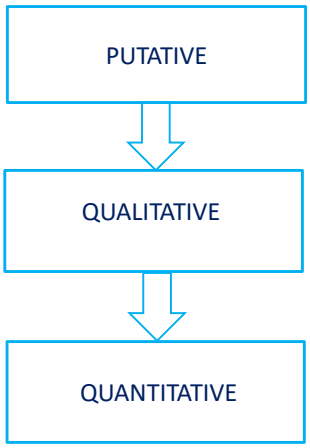
How much change in KE_{up} and/or for how long is needed to evoke some unit of change in KE_{down} ?

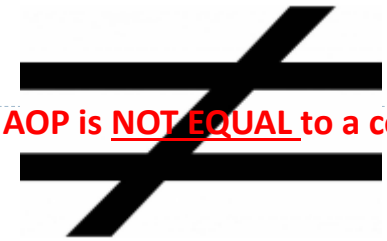


Nature of the response-response relationship



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.

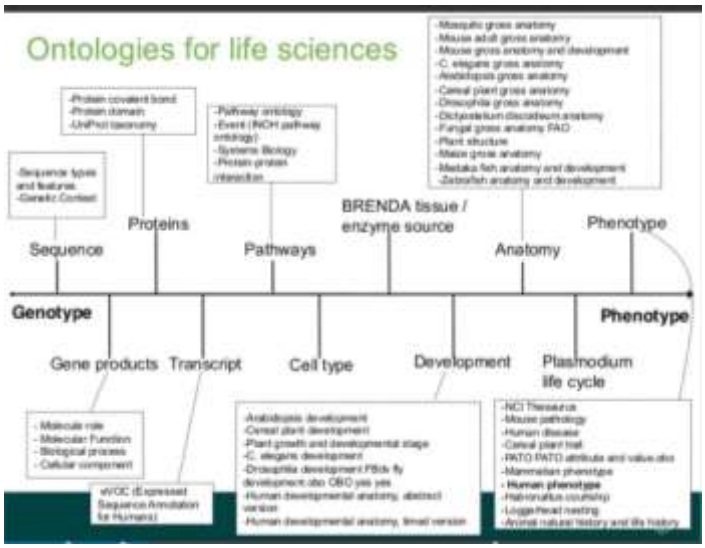
The choice of the modeling method is dependent on the addressed question and the available data

European Commission

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

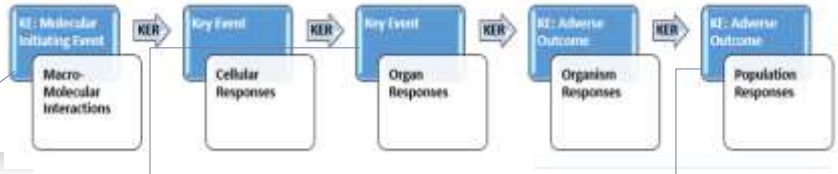
Why add ontology terms in the AOP Wiki ?

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)

- **Process**
- **Object**
- **Action**
- **Context (Cell or Organ term)**

Ontology terms

Ives et al, Creating a Structured AOP Knowledgebase via Ontology-Based Annotations, Applied In Vitro Toxicology (under Press)

Event: 97

Key Event Title

Alkylation, DNA

Short name

Alkylation, DNA

Biological Context

Level of Biological Organization
Molecular

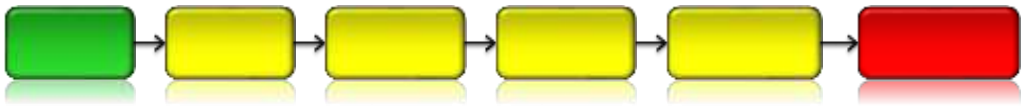
Cell term

Cell term
eukaryotic cell

Key Event Components

Process	Object	Action
DNA alkylation	deoxyribonucleic acid	increased

https://aopwiki.org/events/97

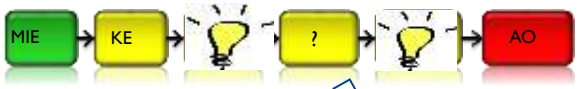


What are AOPs good for?

AOPs

repository

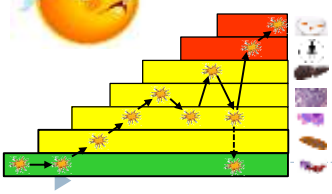
clear presentation



understanding

alternative tests

biomarker



mixtures

terminology

further research

European Commission

AOPs in regulatory context

Chemical Categorisation

Priority Setting for further testing

Read Across

Hazard Identification and Hypothesis-driven Testing

Inter-Species Extrapolation

IATA (Integrated Approaches to Testing and Assessment)

Development of predictive models

Environmental Monitoring

Building Block in MoA Analysis

Mechanistic Support for epidemiological studies

European Commission

Every AOP is useful

Integration of various types of information is necessary for risk assessment

KEY MESSAGES

AOPs are living documents for collaboration and managing collective knowledge

European Commission

AOP knowledge base

BETTER POLICIES FOR BETTER LIVES

https://aopkb.oecd.org/

Wiki Training

European Commission

AOP Knowledge Base

Adverse Outcome Pathway WIKI

AOPs Under Development

- AhR activation leading to embryo toxicity in fish
- Androgen receptor antagonism leading to adverse effects in the male foetus (mammals)
- Androgen receptor antagonism leading to reproductive dysfunction
- Binding to glutamatergic ionotropic receptors can trigger neuroinflammation leading to neurodegeneration
- Binding of antagonist to N-methyl-D-aspartate (NM… of learning and memory abilities
- Binding of agonists to N-methyl-D-aspartate recept… ath, contributing to reduction (or loss) of cognitive function
- Binding of antagonists to NMDAR can trigger neur…
- Binding to electron chain transfer complexes in the…
- Binding to SH/selen-proteins can trigger neuroinfla…
- Calcium-mediated neuronal ROS production and energy …
- Cyclooxygenase inhibition leading reproductive failure
- Ecdysone receptor (EcR) activation leading to mortality i…
- Estrogen receptor agonism leading to reproductive dysfu…
- Glucocorticoid Receptor Activation Leading to Increased …
- …natotoxicity due to nitroaromatics and N-hydroxyl ani…
- …plex I of the mitochondrial respiration chain lead…
- Inhibition of mGR, Rep… y, and regenerative …
- Kidney toxicity induced … of 5HT2R
- LXR Activation to Liver Steatosis
- Multiple Molecular Initiating … trigger Neuro… ation
- AFB1-M…agen… of Action leading to Hep… ular Ca…
- Na… ading to respiratory failure
- Peroxisomal Fatty Acid Beta-Oxidation Inhibition Lead…
- PPAR alpha activation leading to decreased … upon utero ex…
- PPARalpha-dependent liver c…
- PPARγ activation … to decreased fertility in adult female rodents
- Respiratory Sensitisation/Allergy induced by covalent binding to protei…
- Skin Sensitisation Initiated by Covalent Binding to Proteins
- Sustained AhR Activation leading to Rodent Liver Tumours
- Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals
- VEGF Signaling and Vascular Disruption Leading to Adverse Developmental Outcomes
- PPARα activation leading to impaired fertility in adult male rodents
- Inhibition of Na+/I- symporter (NIS) decreases TH synthesis leading to learning and memory deficits in children

OECD EAGMST internal review

OECD Expert Grou… external revi…

…sement

Joint Meeting approve & declassifiy

Versioning AOP-verX.pdf

Science of the Total Environment 628–629 (2018) 1542–1556

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Review

Harvesting the promise of AOPs: An assessment and recommendations

Annamaria Carusi [a,*], Mark R. Davies [b], Giovanni De Grandis [c], Beate I. Escher [d,e], Geoff Hodges [f], Kenneth M.Y. Leung [g], Maurice Whelan [h], Catherine Willett [i], Gerald T. Ankley [j]

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[b] QT Informatics Limited, Macclesfield SK10 5DS, UK
[c] Science, Technology, Engineering and Public Policy (STEaPP), Boston House, 36-37 Fitzroy Square, London W1T 6EY, UK
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[f] Safety and Environmental Assurance Centre, Unilever, Colworth Science Park, Sharnbrook, Bedfordshire MK44 1LQ, UK
[g] The Swire Institute of Marine Science and School of Biological Sciences, The University of Hong Kong, Pokfulam, Hong Kong, China
[h] European Commission, Joint Research Centre (JRC), Ispra, Italy
[i] The Humane Society of the United States, 700 Professional Drive, Gaithersburg, MD, 20879, USA
[j] US Environmental Protection Agency, 6201 Congdon Blvd, Duluth, MN 55804, USA

Thank you

Any questions?

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European Commission, Joint Research Centre (JRC).
maurice.whelan@ec.europa.eu
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European Commission