The European Commission’s science and knowledge service

Joint Research Centre

Maurice WHELAN

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.
JRC sites

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

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

JRC 10 Priority Nexus

1. Economy, finance and markets
2. Energy and transport
3. Migration and territorial development
4. Data and digital transformations
5. Civil security
6. Education, skills and employment
7. Innovation systems and processes
8. Food, nutrition and health
9. People, governance in multicultural and networked societies
10. Resource scarcity, climate change and sustainability
Making scientific evidence available for EU policy

The European Union Reference Laboratory for Alternatives to Animal Testing

- Research
- Validation
- Dissemination
- Promotion
Adverse Outcome Pathways

Maurice Whelan
Francqui Chair 2017-18
Vrije Universiteit Brussel
20th March 2018
"Toxicity pathway"

BORIC ACID

SVHC SUPPORT DOCUMENT

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
"Progress in science depends on new techniques, new discoveries and new ideas, probably in that order."
– Sydney Brenner
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

Exploiting knowledge

Stakeholder Appeal

Applications
Adverse Outcome Pathways (AOP)

- **Key Event (KE)**
- **Key Event Relationship (KER)**
- **Molecular Initiating Event (MIE)**
- **Adverse Outcome (AO)**

Pathogenesis / time
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


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

A. LXR Activation ... Steatosis ... Steatohepatitis ... Fibrosis ... Cirrhosis ... HC Carcinoma
   Multiple AOs in a single, sequential progression = single AOP

B. LXR Activation ... Steatosis ... Steatohepatitis ... Fibrosis ... Cirrhosis ... HC Carcinoma
   Branching = two AOPs

Liver failure

HC Carcinoma
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
Developing organism

\[ \text{MIE} \rightarrow \text{KE}_1 \rightarrow \text{KE}_2 \]

Adult organism

\[ \text{MIE} \rightarrow \text{KE}_1 \rightarrow \text{KE}_2 \]

Male

\[ \text{KE}_1 \rightarrow \text{KE}_2 \rightarrow \text{KE}_3 \rightarrow \text{KE}_4 \]

Female

\[ \text{KE}_1 \rightarrow \text{KE}_2 \rightarrow \text{KE}_3 \rightarrow \text{KE}_4 \]

In liver

In lung

In brain

Adjacent/non-adjacent KERs

\[ \text{non-adjacent KER} \rightarrow \text{adjacent KER} \rightarrow \text{adjacent KER} \rightarrow \text{adjacent KER} \rightarrow \text{adjacent KER} \rightarrow \text{non-adjacent KER} \]
Quantitative Understanding of KERs

➢ Response – response relationships
➢ Time – scale
➢ Known modulating factors
➢ Known feedback/feedforward loops influencing KER

熟知反馈/前馈循环影响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

- PUTATIVE
- QUALITATIVE
- QUANTITATIVE

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)

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
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)

AOPWiki

Event: 97
Key Event Title
Alkylation, DNA

Short name
Alkylation, DNA

Biological Context

- Level of Biological Organization: Molecular
- Cell term: eukaryotic cell

Key Event Components

<table>
<thead>
<tr>
<th>Process</th>
<th>Object</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA alkylation</td>
<td>deoxyribonucleic acid</td>
<td>increased</td>
</tr>
</tbody>
</table>

https://aopwiki.org/events/97
What are AOPs good for?
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

Every AOP is useful
Integration of various types of information is necessary for risk assessment

KEY
AOPs are living documents for collaboration and managing collective knowledge

MESSAGES
AOP Knowledge Base

OECD EAGMST internal review
OECD Expert Group external review
Joint Meeting approve & declassify

https://aopkb.oecd.org/

Wiki Training
Review

Harvesting the promise of AOPs: An assessment and recommendations

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Thank you

Any questions?

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