AOP ACTIVITIES AT THE OECD

Workshop AOPs: From Research to Regulation
3 - 5 September 2014

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Launch of the Programme at OECD

• The AOP Development Programme was launched at OECD in 2012, under the umbrella of the Advisory Group on Molecular Screening and Toxicogenomics (Programme on Chemical Safety).

• AOPs are a central concept in future work at OECD on predictive toxicology, improving uses and applications of mechanistic information for both future testing and assessment needs.

• Several OECD groups are involved, interdisciplinary nature of the work
The OECD programme on the development of AOPs addresses the needs of:

- the OECD Test Guidelines Programme for the identification of new *in vitro* test methods that are candidates to become OECD Test Guidelines;
- The OECD QSAR Project for the identification of new methods/profilers for grouping chemicals;
- the OECD Hazard Assessment activities for the development of IATAs for defined hazard endpoints.
Framework for the development and use of IATAs

• Approaches to decide on the adverse effect of a chemical by using existing information, alternative methods and tailored testing strategies.

• Starts with the formulation of plausible and testable hypotheses about the toxicological potential of a chemical based on existing information and/or information derived from lower tier testing.

• The information would then be used to evaluate data gaps and what testing approaches if any would be most appropriate to undertake in order to elucidate the toxicological profile of that substance
Integrated Approaches to Testing and Assessment (IATA)

- The vision is that the results from appropriate combinations of selected *in silico*, *in chemico*, and *in vitro* tests that target key events along well defined AOPs could provide sufficient information for hazard and risk assessments with minimal, but well-tailored need for further testing.

- The knowledge of an adverse outcome pathway or mode of action can provide the scientific framework for developing and using IATAs.
AOPs/MoAs could be used to:

• develop (Q)SARs
• support grouping of chemicals into chemical categories for subsequent data gap filling for a specific endpoint using read-across or trend analysis
• develop testing strategies
• select methods for TG development
• interpret results from non-standard test methods
Use of the AOP concept to categorise chemicals for a specific endpoint
Use of an AOP to develop QSARs

Diagram showing the relationship between MIE, KE 1, KE 2, KE n, and AO.
Use of an AOP/MoA in a testing strategy

TIER 1
- Positive
- Equivocal
- Negative

TIER 2
- In vitro assay 1
  - Positive
  - Negative
  - Equivocal

TIER 3
- In vitro assay 3
  - Positive
  - Negative

MIE
KE 1
KE 2
AO
OECD Workshop on a framework for the development and use of IATA

Aim

• To test the applicability of the AOP/MoA concept as a framework for developing and using IATAs and to refine the framework as far as possible.
• Build consensus that the AOP/MoA concept is a good basis for developing and using IATAs,
• Determine for which type of IATA, the AOP/MoA concept can be used,
• Discuss and refine different stages of development of an AOP
• Decide which of the different stages is most suitable for each type of IATA and their associated purpose.
Relevant documentation published at OECD

- Template format for project proposals

- Guidance document on developing and assessing AOP (2013), No. 184 Series Testing and Assessment

- User handbook (more practical and wiki-oriented than the guidance, under preparation)
Functioning of the AOP Development Programme at OECD

• The OECD Advisory Group on Molecular Screening and Toxicogenomics (EAGMST) is a large group of experts from various areas of toxicology.

• Experts are designated by governmental or non-governmental affiliations (academia, agencies, industry, animal welfare groups, scientific societies, etc.)

• The EAGMST meets once a year before summer and holds a teleconference, usually in December to keep pace with new developments.
Functioning of the AOP Development Programme at OECD

- **Project proposals** to develop new AOPs can be made by members of EAGMST or the public (academia, scientific societies, industry groups, etc.)

- **Project proposals** can be submitted any time of the year to the Secretariat who makes them available to the EAGMST for their review.

- The AOP Development Programme maintains a rolling work plan, updated twice a year with new project proposals and new information on existing projects.
  - Twice a year, project proposals are reviewed and included in the work plan if justified and in line with the objectives of the Programme.
Where can I find relevant information?

- A public web-page provides summary information to the public on the AOP development programme, including titles of AOP on the workplan and lead organisations/countries, relevant templates for making proposals, guidance on how to develop AOPs, etc.

Where can AOPs under development be found?

• A **wiki-based** interface has been developed to enable AOP description (MIE, KE, KER, AO)
  • [http://aopwiki.org](http://aopwiki.org)
    → *see Stephen Edwards presentation*

• The AOP wiki will be **publicly launched** by end of September 2014

• All AOPs should be considered at this stage as drafts under development
PROPOSED PROCESS FOR THE DEVELOPMENT OF AOPs
(This is work in progress and might be revised based on experience gained)

1. Lead country/organisation
2. Project proposal for development of an AOP
3. Review of proposals
4. Annual meeting of the Extended Advisory Group
   - Public input (e.g., scientific societies)
5. OECD Expert Groups are invited to provide input and comments
6. If positive decision
7. Project included in the AOPD workplan
8. AOP KB
   - Wiki-based platform to generate the descriptive document
   - Graphical Interface (Effectopedia)
9. Effects database
   - Links to AOP KB
10. At OECD
11. Partnership EU JRC-US EPA-OECD
12. Back to OECD
13. 3rd draft
14. 2nd draft
15. 1st draft AOP Descriptive document by the lead country or organisation
16. Consultation process in view of endorsement
17. Extended Advisory Group Molec. Screening TGX
18. WNT (National Coordinators Test Guidelines)
19. Task Force Hazard Assessment
20. Submitted to WNT for endorsement

Partnership EU JRC-US EPA-OECD
At OECD

Effects database

Back to OECD

Partnership EU JRC- US EPA-OECD

Document is submitted to WNT and TFHA for endorsement

Endorsement by the WNT and TFHA

Submission

Declassification by the Joint Meeting

Implementation of AOP in QSAR Toolbox by the QSAR Management Group, under the Task Force on Hazard Assessment

Lead country or organisation: Proposal for Integrated Testing Strategy under the TFHA

Lead country or organisation: Identification of possible Test Guidelines to be developed under the WNT

AOP descriptive document published
Status of AOPs developed at OECD

- AOPs are **scientific descriptive documents** depicting interactions, events, outcome, etc.: as such, they have **no regulatory implication**

- AOP can be developed in parallel of scientific publications (OECD work **does not preclude scientists to publish** in the literature)

- AOPs can be seen as continuously developing, and **OECD-agreed versions of AOPs can evolve** as science progresses
Conclusions and take home messages

• AOP Development Programme is evolving fast with participation of multiple groups of experts in various areas of toxicology.

• The public can make project proposals to develop AOPs (published guidance for users).

• AOPwiki soon publicly available (end Sept. 2014) to enable crowd-sourcing.
Organizing the adverse outcome pathways knowledge – the Effectopedia way.

Hristo Aladjov, 27 August, Prague
Visually Express Biological Context

Cause A → Link → Effect B

mid term - cellular

short term - tissue
Effectopedia’s Pathway Space

- Life stage
- Taxonomy
- Gender
- Generation
- Time to effect
- Level of biological organization
- ...

- User expandable set of biological context dimensions
- Interface allows easy switching between pathway space 2D projections
Pathway elements

**Chemical Substance**
- Link
- MIE

**In-Silico Test Method**
- Applicability domain
- Executable source code
- Training Set
- Verification Set

**In-Chemico Test Method**
- Guideline Ref.
- Formal (ISAtab) assay description
- Applicability domain
- Set of tested chemical compounds

**In-Vitro Test Method**
- Guideline Ref.
- Formal (ISAtab) assay description
- Applicability domain
- Set of tested chemical compounds

**In-Vivo Test Method**
- Guideline Ref.
- Formal (ISAtab) assay description
- Applicability domain
- Set of tested chemical compounds
Pathway elements – test response mapping

In vivo effect

Concentration, [Log M]

Test response mapping (function)

Measured effect

Concentration, [Log M]
Pathway elements

- **Chemical Substance**
- **MIE**
- **Biological Effect**
- **Adverse Outcome**

**Links**:
- Hypothetical Dose-response
- Direct Threshold Response-response
- Hypothetical

**In-Vitro**
- Comp1 Obs. 1
- Comp1 Obs. 2
- Comp2 Obs. 1
- CompN Obs. 1

**In-Vivo**
- Comp1 Obs. 1
- Comp2 Obs. 1
- CompM Obs. 1
- CompL Obs. 1

**Effect**

**Mid-term**

**Long-term**

**Levels**
- Molecular
- Organelle
- Cellular
- Organ system
- Individual
FUTURE PENETRATION MODELS AND METABOLISM

Individual exposure route

Organ 1 Penetration PhKM

Available Substance

Tissue 1 Penetration PhKM

Available Substance

Tissue 2 Metabolic Activation

Available Metabolite 1

Available Metabolite 2

Target Site Penetration PhKM

Available Substance

Target Site Penetration PhKM

Metabolite 1

Metabolite 2

Parent Substance

MIE

In-Vitro Comp 1 Obs. 1
Comp 1 Obs. 2
Comp 2 Obs. 1
Comp N Obs. 1

In-Vivo Comp 1 Obs. 1

biosphere population

individual

organ system

organ

tissue
cellular

tissue

organelle

molecular

molecular

organelle