New approaches to building chemical categories

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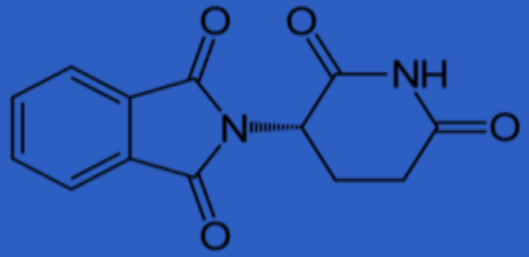
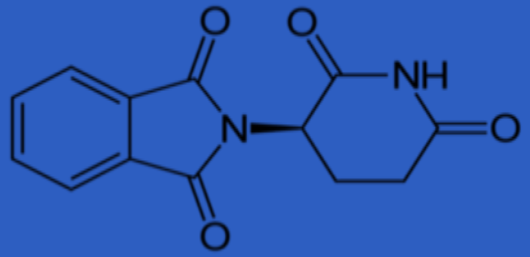
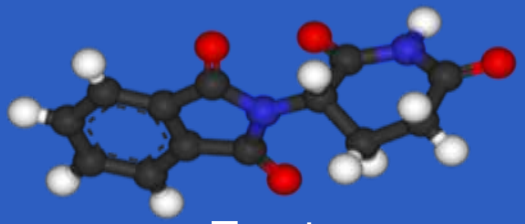
Concawe Symposium

Feb 2015

One of these things is not like the others …



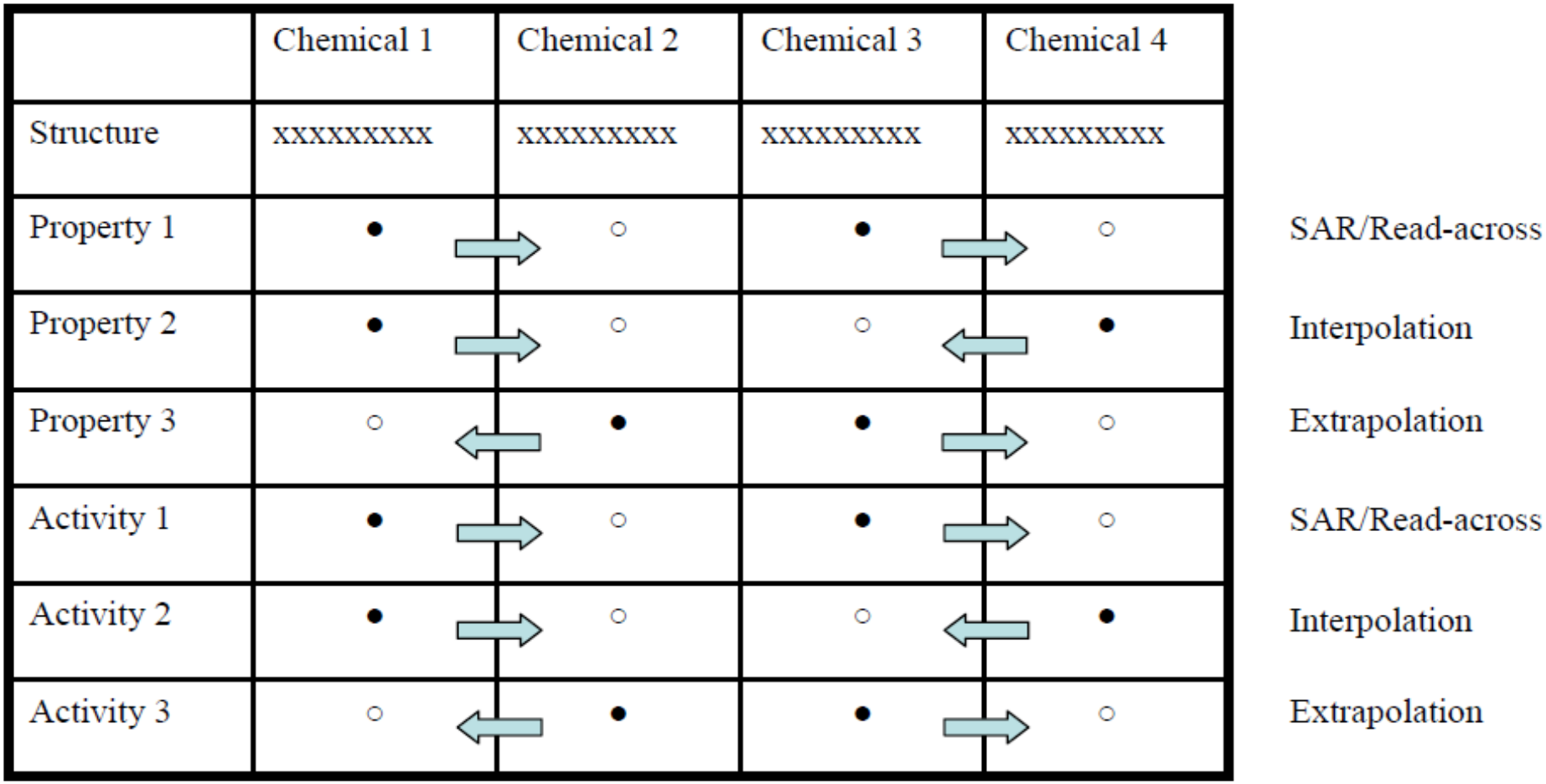




Teratogen

Sedative

Figure 1. Graphical representation of a chemical category and some approaches for filling data gaps



Guidance on Grouping of Chemicals
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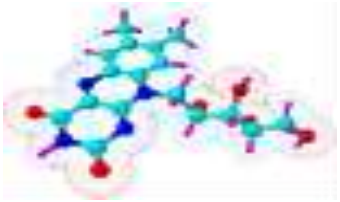
Sources of similarity descriptors



- Chemical identity and composition
  (structure, composition, impurities, functional groups)
- Physical-chemical properties and other molecular descriptors
- Kinetics: Absorption, distribution, metabolism and excretion
- Mode/Mechanism of action or adverse outcome pathways
- Chemical / biological interaction
- Responses found in alternative assays
- Information obtained from other endpoints/species/routes

Source:
Guidance on Grouping of Chemicals 2nd Edition OECD ENV/JM/MONO(2014)4

European Commission

Unclassified **ENV/JM/MONO(2014)4**

Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

14-Apr-2014

*"To use a **mode of action argument in support of a category**, there needs to be consensus that it is a suitable and valid approach. With the increasing availability of mode of action information, adverse outcome pathways (AOP) and high throughput screening (HTS) as well as other predictive data, more integrative approaches can be explored to support hypotheses for read-across and selection of the most appropriate molecular descriptor(s)."*

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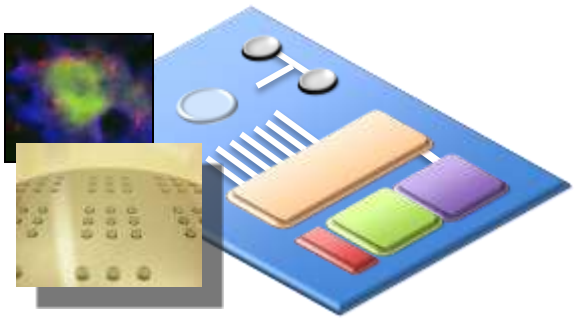
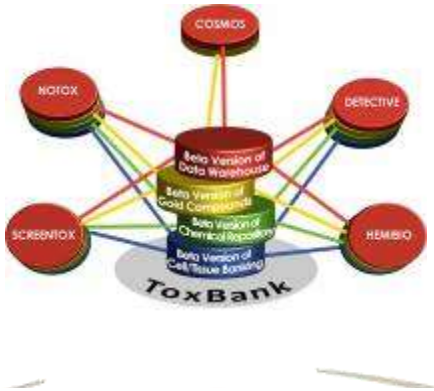
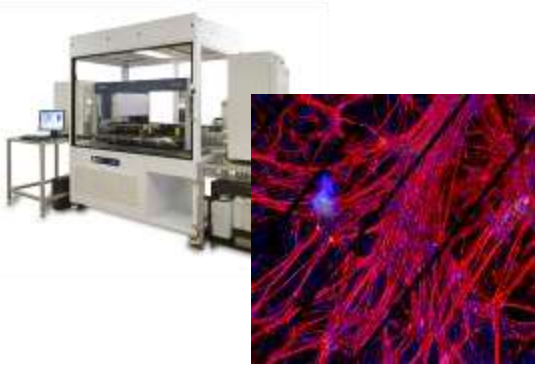
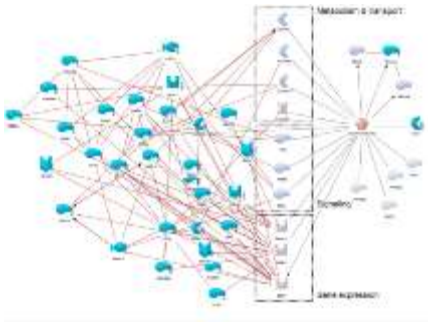
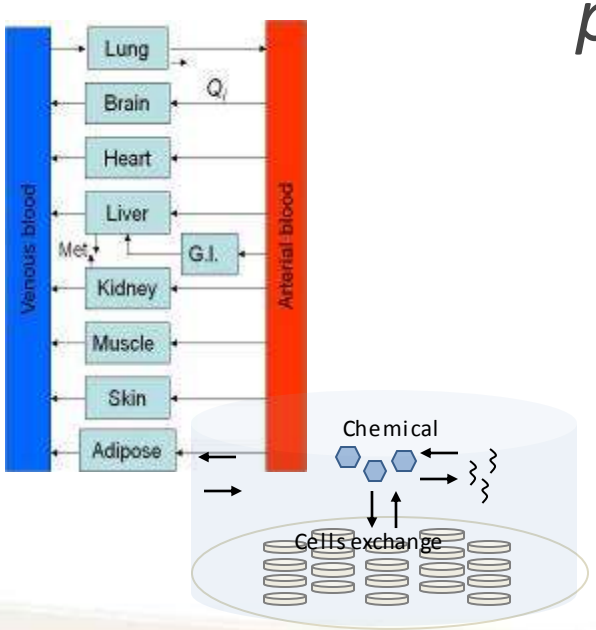


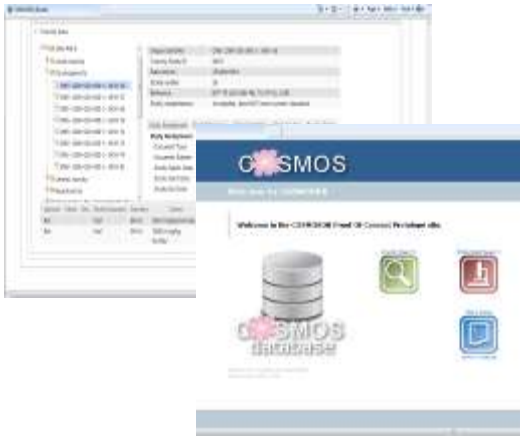


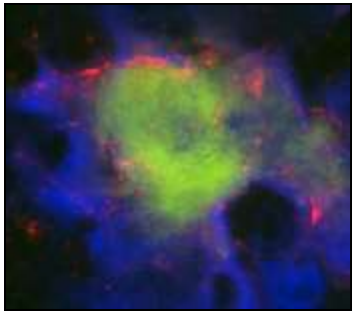


Project data and protocol warehouse





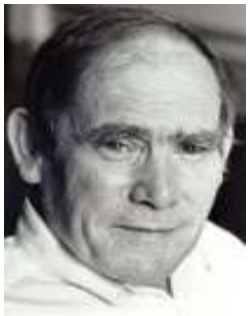




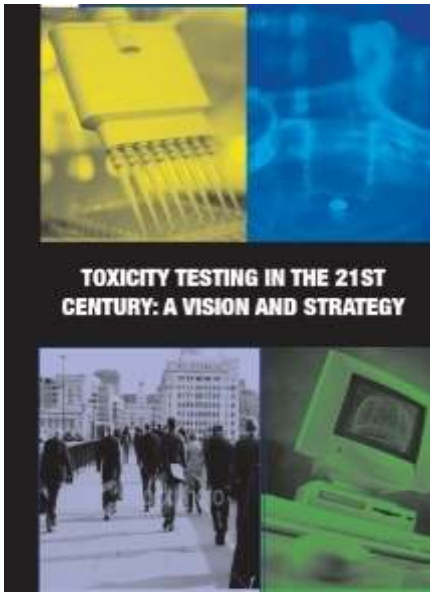
… intelligent integration towards informed decision making

"We now have unprecedented ability to collect data about nature but there is now a crisis developing in biology, in that completely unstructured information does not enhance understanding. We need a framework to put all of this knowledge and data into - that is going to be the problem in biology. We've reached the stage where we can't talk to each other - we've all become highly specialized. … driving toward that framework is really the big challenge."

- Sydney Brenner. Molecular Biologist and Nobel Laureate,
NIH-BISTI Symposium 2003



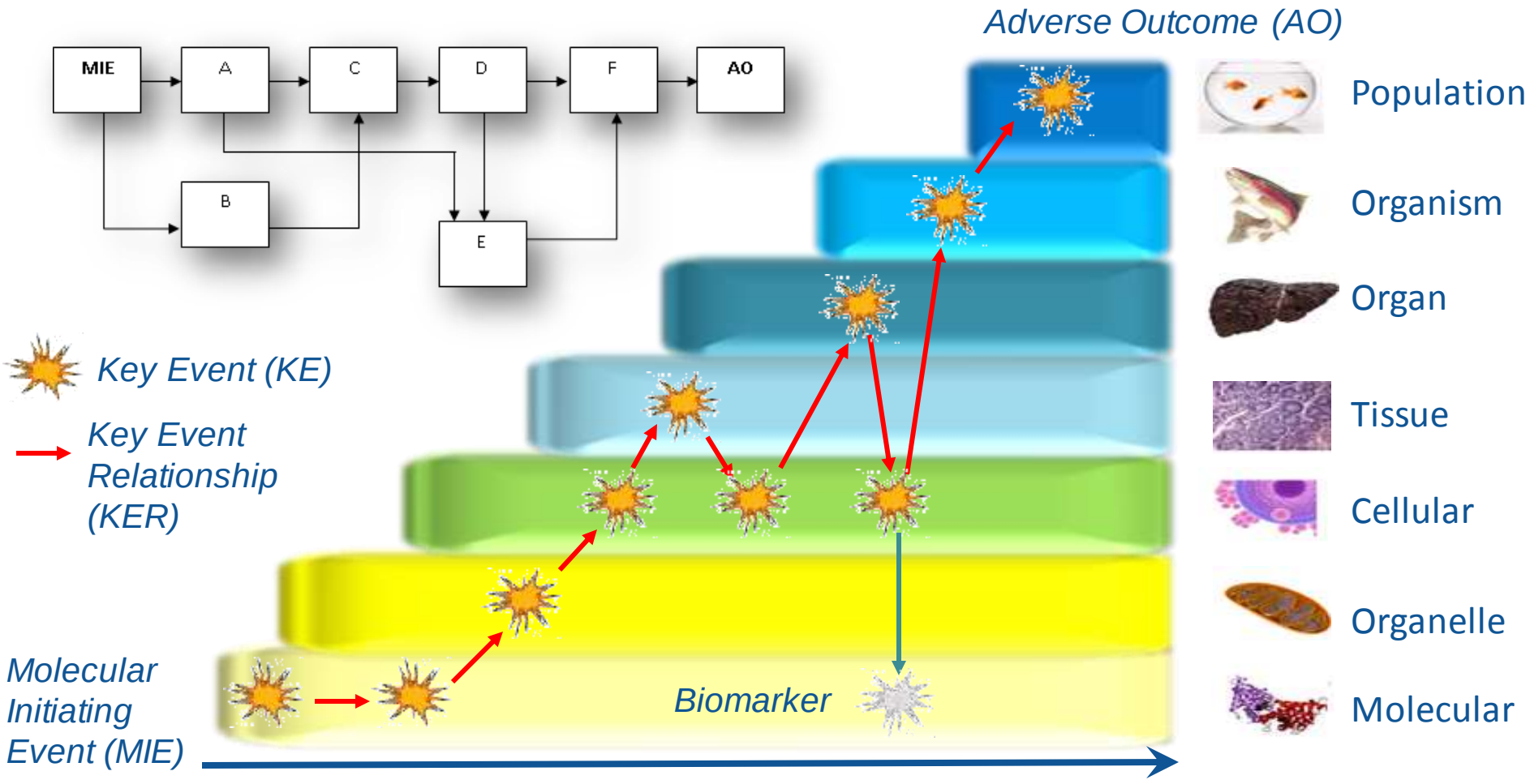
Toxicity Pathways
(NRC 2007)



WHO/IPCS Mode of Action Framework
(Meek et.al. 2013)

Adverse Outcome Pathways
(Ankley et. al. 2010)

AOP: discretized multiscale process



AOP Networks

AOP is the functional unit of an AOP network

AOPs are 'linear' but the network is not

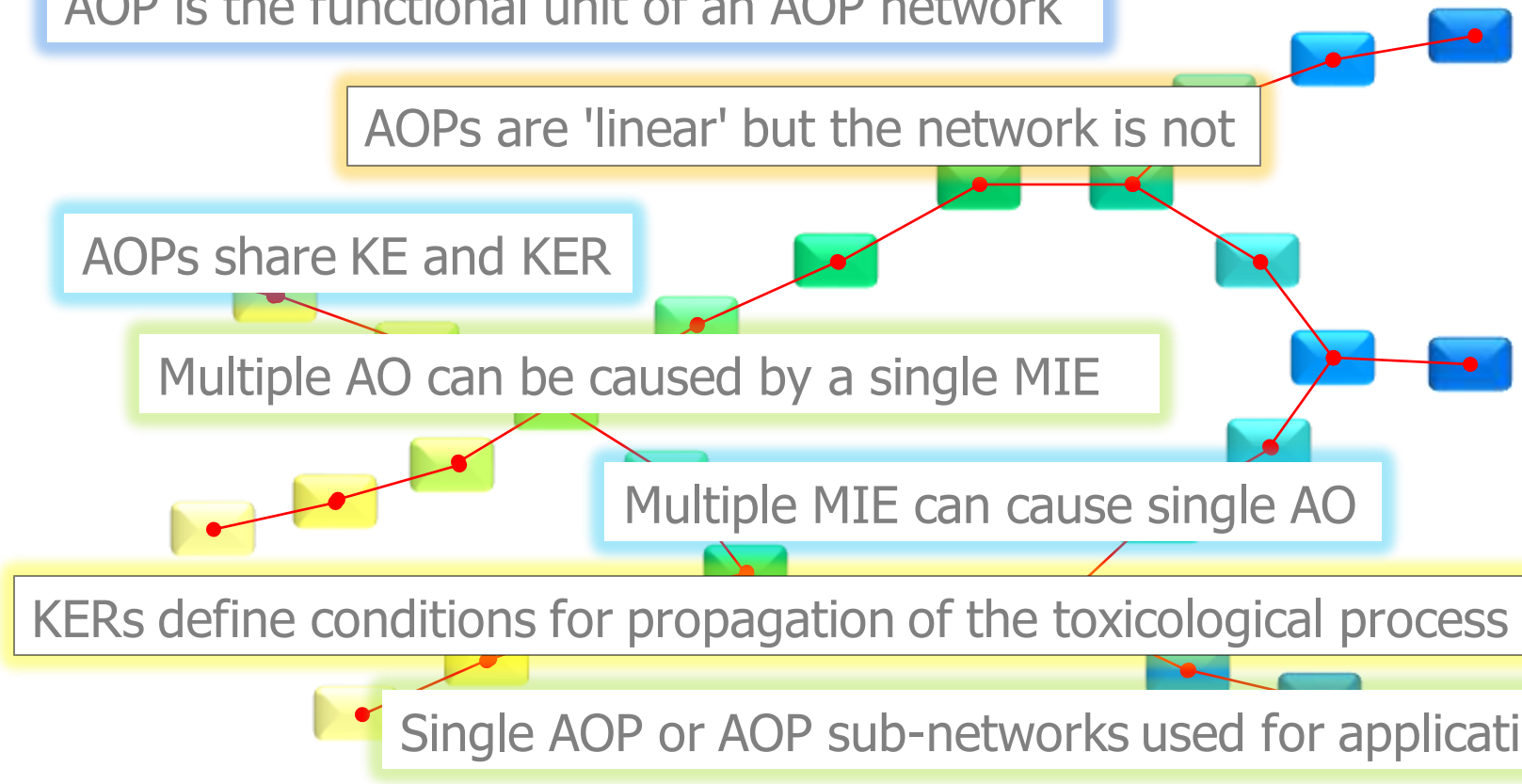
AOPs share KE and KER

Multiple AO can be caused by a single MIE

Multiple MIE can cause single AO

KERs define conditions for propagation of the toxicological process

Single AOP or AOP sub-networks used for application

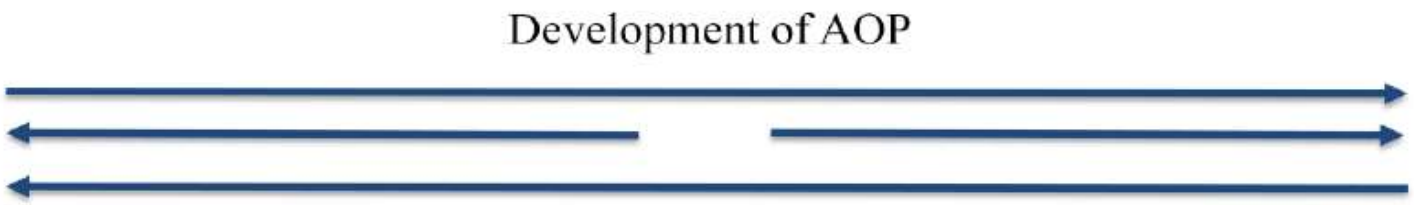


Nodes represent Key Events (KE)
Edges represent Key Event Relationships (KER)

OECD AOP Development Programme

Responsibility of the Extended Advisory Group on Molecular Screening and Toxicogenomics (EAGMST)

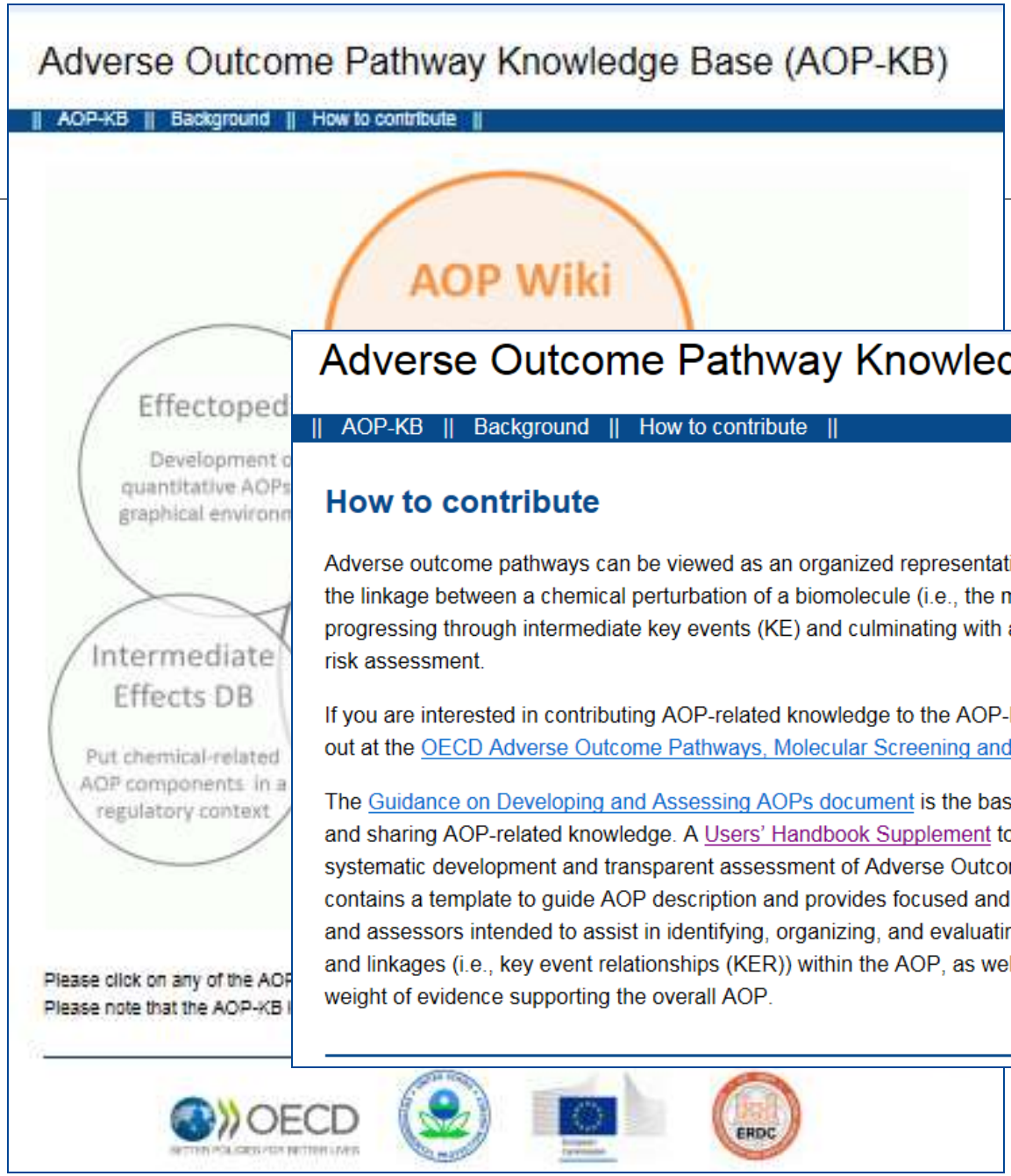
Co-chairs: Robert Kavlock (US EPA) & Maurice Whelan (EC JRC)



Villeneuve et. al., (2014) 'Adverse Outcome Pathway (AOP) Development I: Strategies and Principles', *Toxicol. Sci.,* 142 (2): 312-320 doi:10.1093/toxsci/kfu199

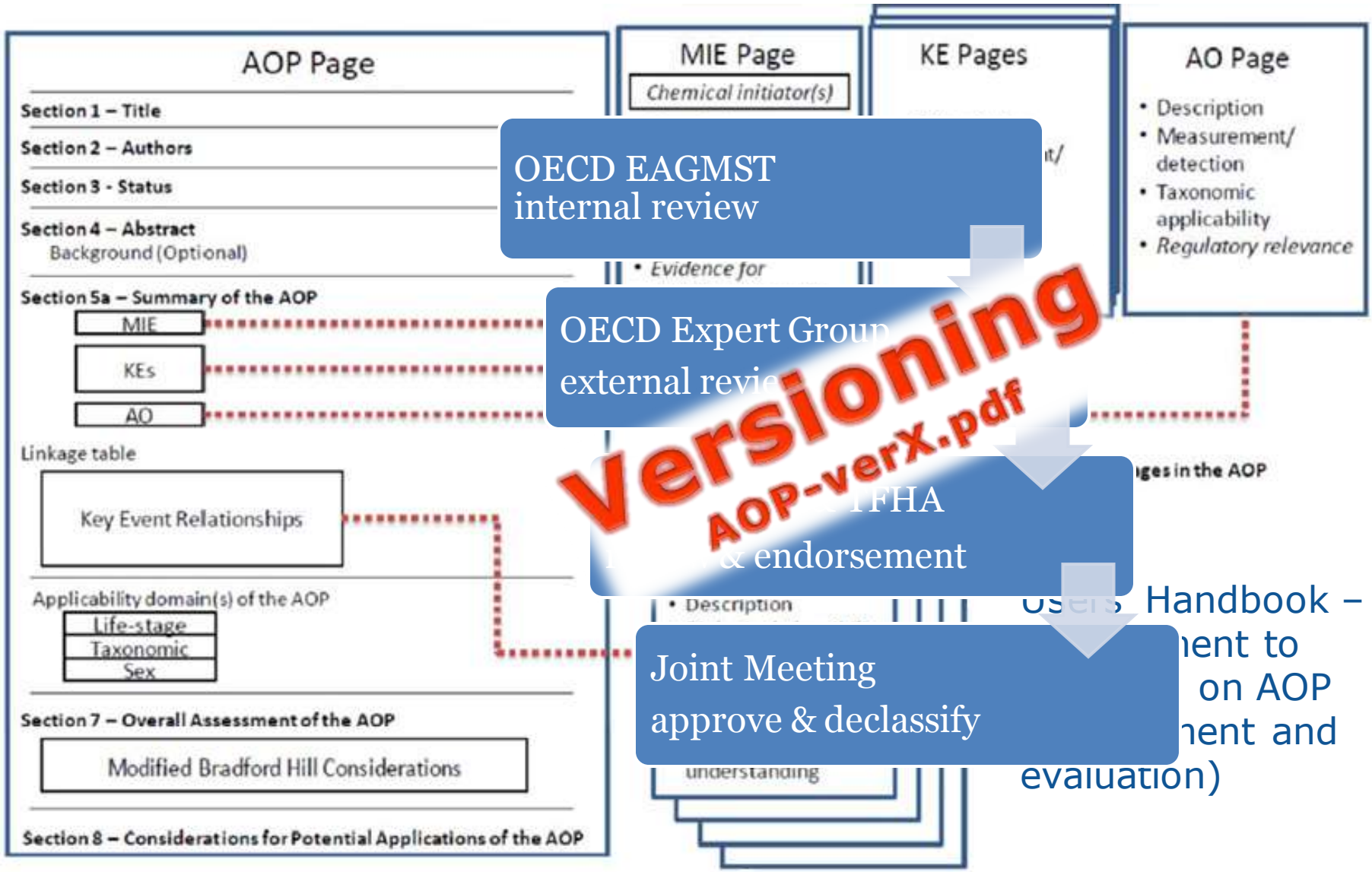
Villeneuve et. al. (2014), 'Adverse Outcome Pathway (AOP) Development II: Best Practices', *Toxicol. Sci.,* 142 (2): 321-330 doi:10.1093/toxsci/kfu200

OECD Template and Guidance on developing and assessing the completeness of Adverse Outcome Pathways (2013); Supplementray 'User Handbook' (Sept 2014).



www.aopkb.org

AOP Wiki – Document (Article) structure



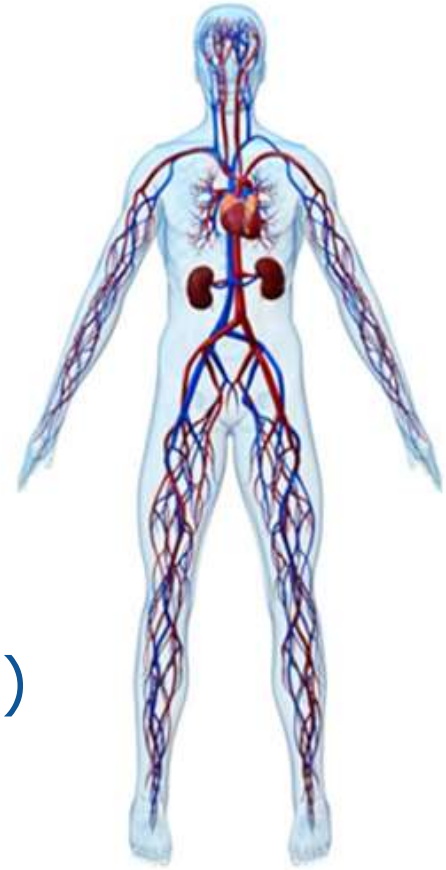
Building AOP based categories

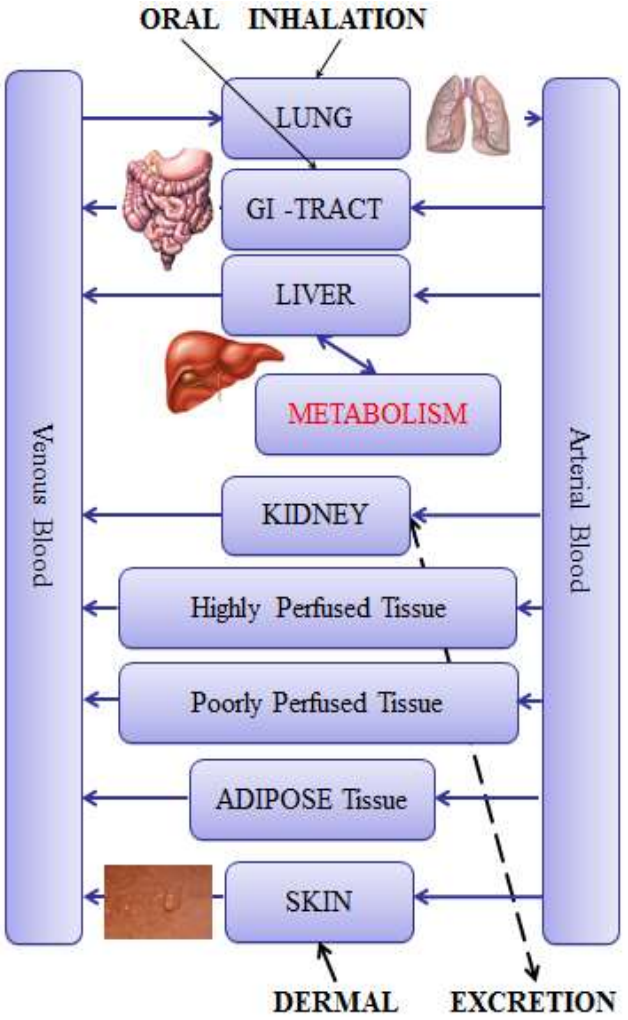
	Molecular Initianig Event							Intermediate Events								Adversity										
	ER	GR	PPARalpha	PPARbeta /delta	PPARγ	AR	AhR	Sertoli	spermatocyte maturation	Leyding	change testosterone	Testicular zinc concentration	Seminiferous tubules	Androgen binding protein	steroidogenesis genes	reproductive organs	general toxicity/ Maternal toxicity	Reproductive performance	Offspring viability	Male reproductive tract abnormalities	Abnormalities of sperm parameters	Internal, visceral, skeletal malformation	Genitalia malformations	Change ano-genital distance	Nipple retention	Abnormalities of liver	Abnormalities of kidney
Diethyl phthalate (DEP)	0									1	1				0	0	1	0	0	0	/	0		0		1	0
Diisobutyl phthalate	1							1	1	1	1		1		1		0		/	1		1	1	1	1		
Di-n-pentylphthalate (DPP)	0							1	1		1	1	1	1	1		0	1	1	1	1			1	1	/	0
Dicyclohexyl phthalate (DCHP)	0	1			0			1	1	1	1		1		1		1	0	0	1	1	0	1	1	1	1	1
Dihexyl phthalate (DHP)	0					0		1	1	1	1		1		1		/		1	1	1	1	1	1	1	1	1
Diisononyl phthalate (DINP)	0					0	0	1	1	1	1		0		1		1	0	0	0	1	1		/	1	1	1
Diisodecyl phthalate (DIDP)	0					0	1				0		0		0		1	0	0	/	1	1		0	0	1	1
Di-n-propylphthalate(DnOP)	0											/				1	0	0	0	0	1	1				1	1
Butylbenzylphthalate (BBP)	1		1	1	1	1	1		1	1	1		1			1	1	1	1	1	1	1	1	1	1	1	1
Dpr9																	1	1	1	1	1	/	1	1		1	1
MEHP			/	1	1	1		1	1	1	1		1			1	1		1	1	1	1	1	1		1	
DEHP	/		1	1	1	/	1	1	1	1	1	1	1			1	1	1	1	1	1	1	1	1	1	1	1

Codifying AOP as a bit-string to computerise analogue search

ADME similarity descriptors

- Metabolic profile
- Metabolic pathway
- Half-life
- Tissue distribution
- Percentage absorbed
- AUC, Cmax, tmax
- Time-course (kinetics)
- ....





Visualisation of information

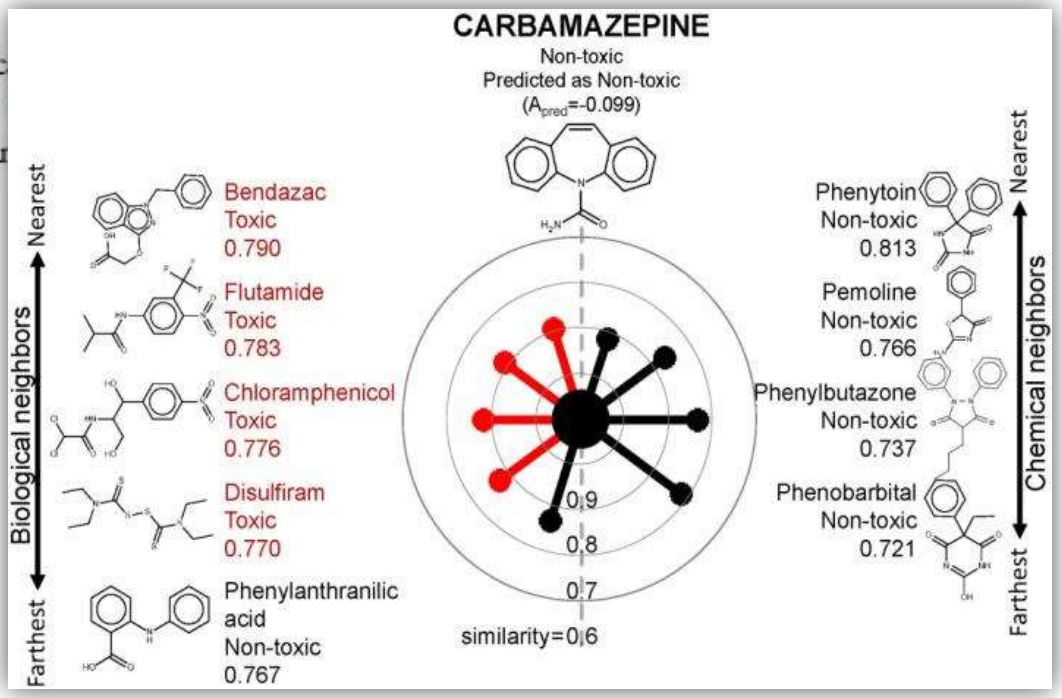
Chemical Research in Toxicology

Integrative Chemical–Biological Read-Across Approach for Chemical Hazard Classification

Yen Low,[†,‡] Alexander Sedykh,[†] Denis Fourches,[†] Alexander Golbraikh,[†] Maurice Whelan,[‡] Ivan Rusyn,*[,‡] and Alexander Tropsha*[,†]

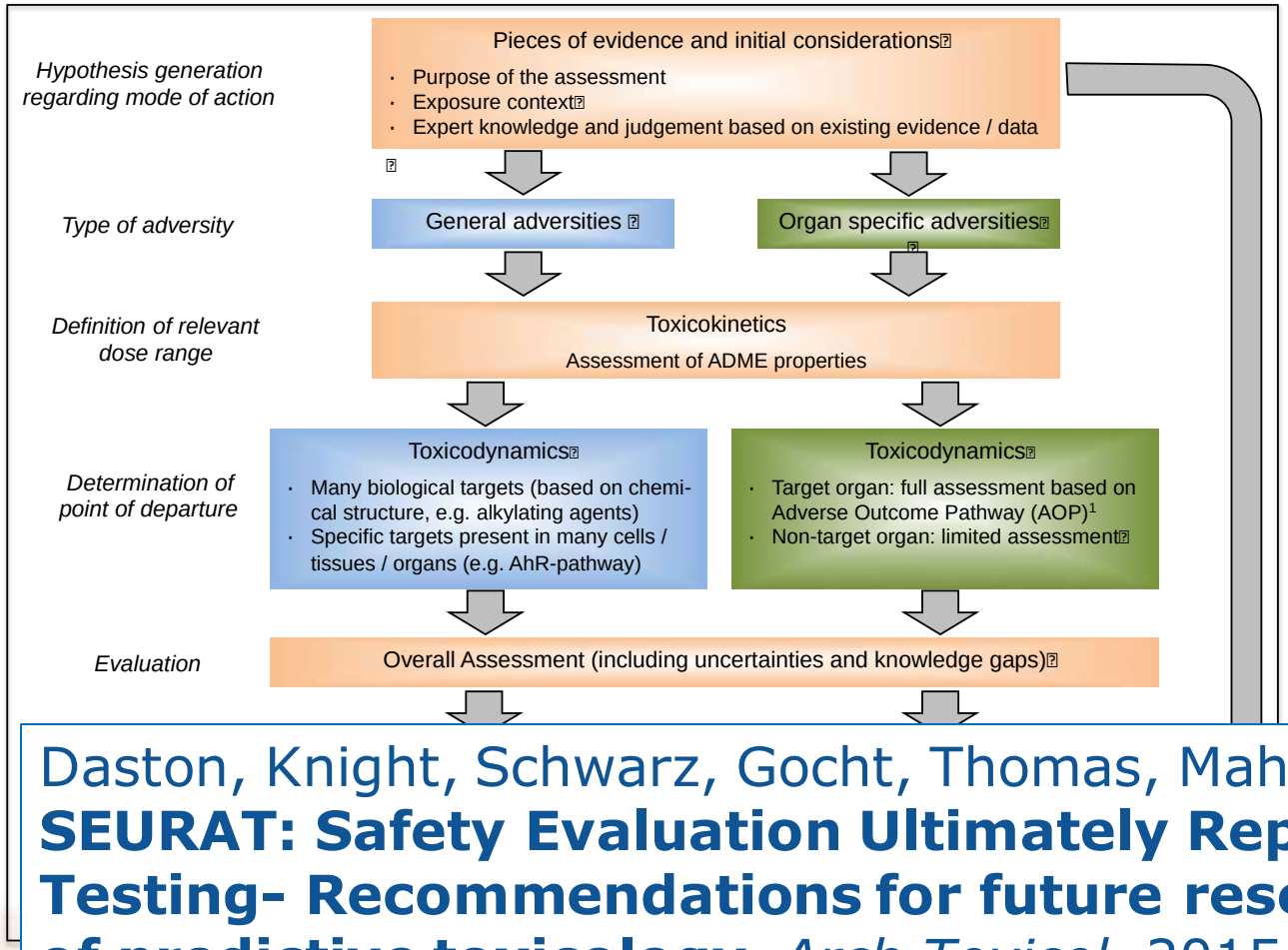
[†]Laboratory for Molecular Modeling, Division of Chemic
Sciences and Engineering, University of North Carolina,
[‡]Systems Toxicology Unit, Institute for Health and Consur
2749, 21027 Ispra, Italy

Visualisation of toxicity prediction from both chemically similar **AND** biologically similar neighbors



Safety assessment case studies

One conceptual framework - three case studies:



Daston, Knight, Schwarz, Gocht, Thomas, Mahony, Whelan; **SEURAT: Safety Evaluation Ultimately Replacing Animal Testing- Recommendations for future research in the field of predictive toxicology**. *Arch Toxicol.* 2015 Jan;89(1):15-23.

Outlook ...

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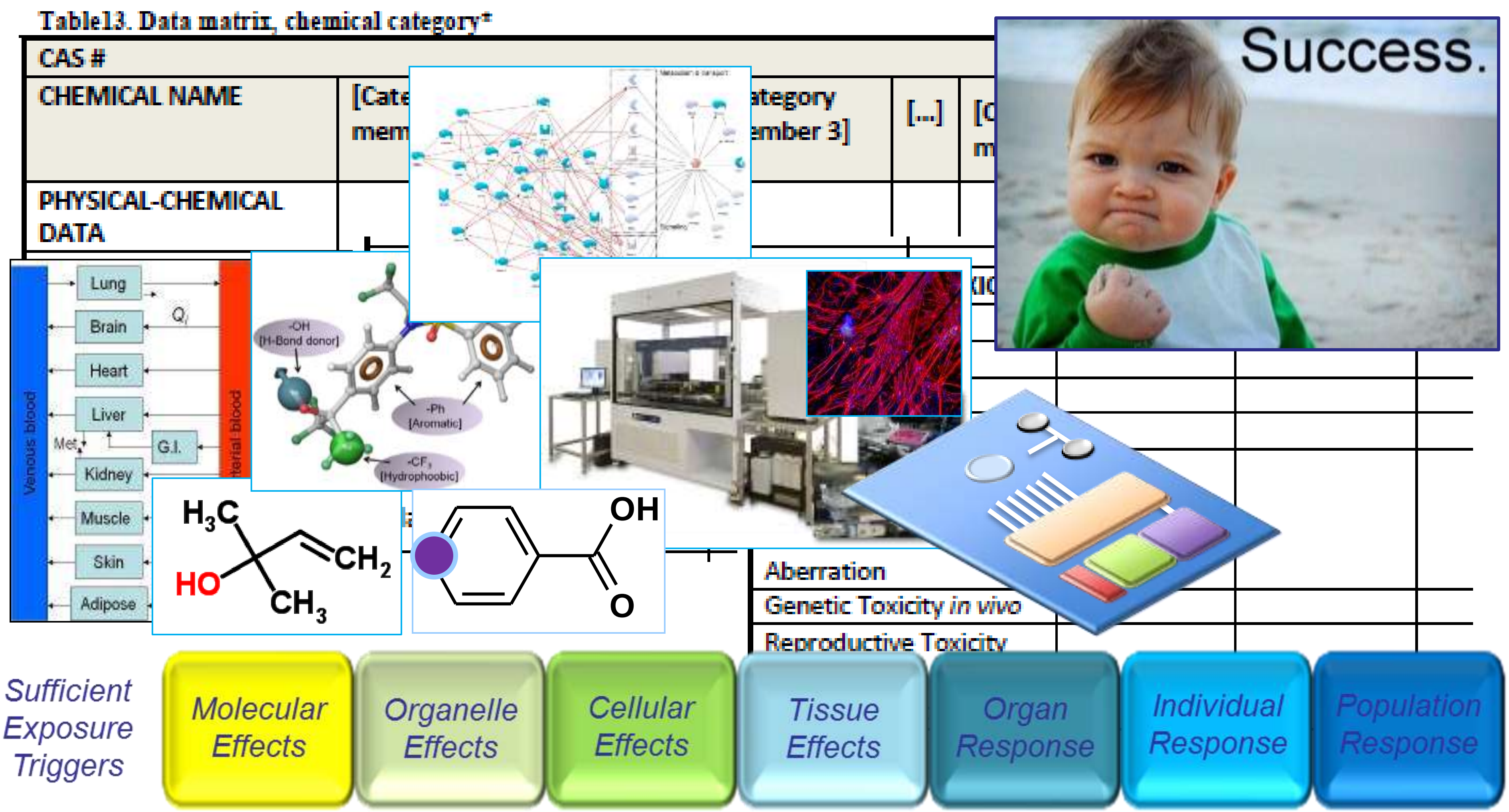
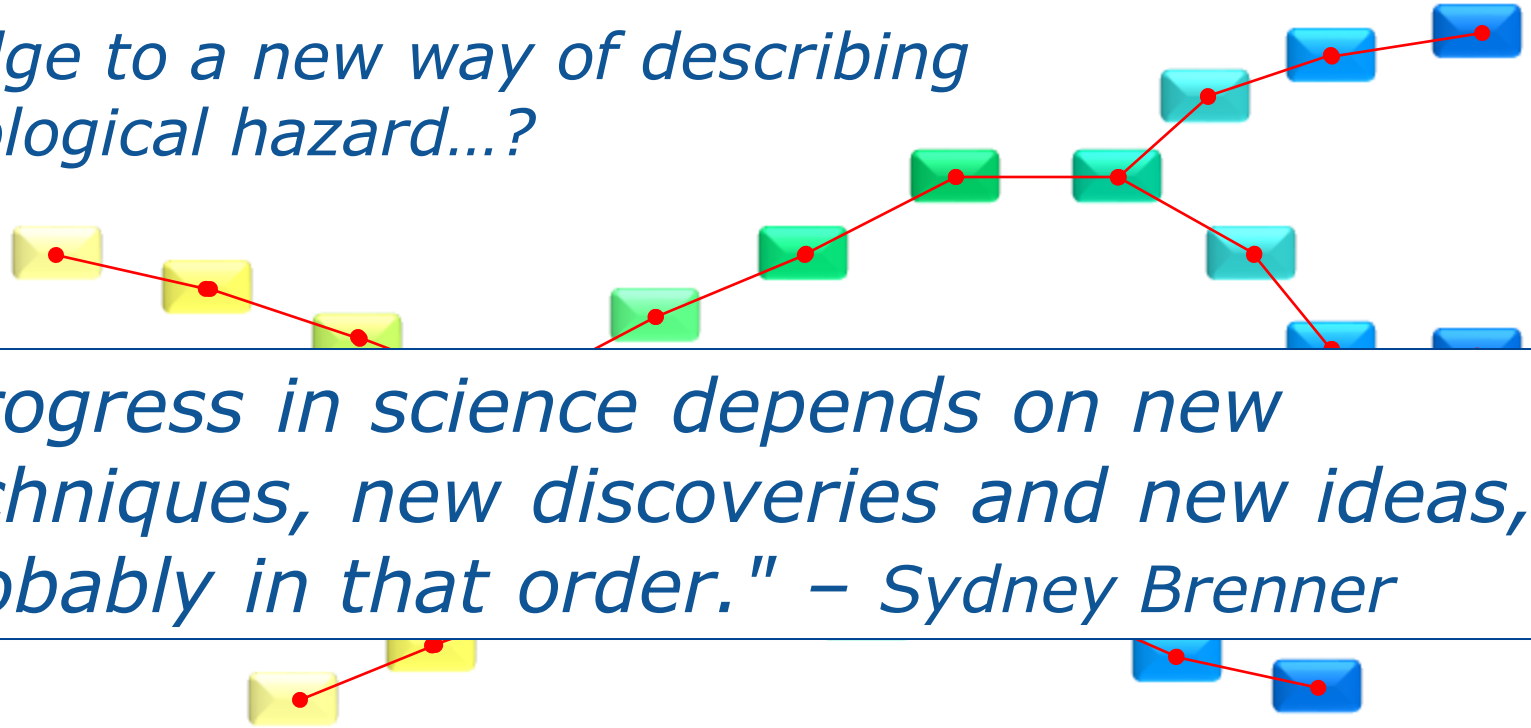


AOP Networks

A bridge to a new way of describing toxicological hazard…?



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

….. based on mechanistic profiling rather than association with pathological 'endpoints'

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