

Master 1 D<sup>2</sup>HP Development of Drugs and Health Products

Compulsory Teaching Unit 11: Pharmacology/Toxicology

## Immunotoxicology AOPs

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# **AOP concept**



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The AOP concept : developed in response to uncertainties in the field regarding usage of the terms mechanism of action and mode of action.



## Exposome

**Exposome** is a concept corresponding to the totality of exposures to external and environmental factors that a human organism undergoes from conception through in utero development to the end of its life, complementing the effect of the genome.



## Danger and risk



Conceptually, an AOP can be viewed as a sequence of events beginning with the initial interactions of a substance with a biomolecule in a target cell or tissue (i.e., a molecular initiating event), continuing through a dependent series of intermediate events, and ending with a negative outcome.

https://aopkb.oecd.org/

Molecular Initiating Event	Key Events $1 \Rightarrow 2 \Rightarrow 3$	Adverse Outcome

## Adverse Outcome Pathways (AOPs)



(Ankley et al., 2010)

- Structure and integrate information on chemicals from the initiating event at the molecular level to the observed adverse effect
  - 2. To guide the implementation of testing strategies in order to develop, prioritize and justify targeted tests
  - 3. Establish the causal links with the observed toxic effects
  - 4. To develop an approach by categories of chemical substances

#### Adverse Outcome Pathways (AOPs)



- **objectives** 1. Structure and integrate information on chemicals from the initiating event at the molecular level to the observed adverse effect
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#### **AOP wiki**

New tool for developing and documenting adverse event pathways Facilitates knowledge sharing

wiki : acronyme de « What I Know Is »

AOP Wiki: information storage, evaluation, and linkage

Publically accessible since September 2014 www.aopwiki.org http://www.aopwiki.org/

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OP-Wi	ki AOPs Key Events	KE Relationships	Prototypical Stressors	s Developers' Hand	ibook			
liver		Search	Find by ID	Find	l by ID			
				With OECD status	With SAAOP status	Recent AOPs		
AOP	Title Search Res	ults						
Filtere	d AOP Count: 13							? 😿
	Title 🖨	Point of Contact 🖨	Author Status 🖨	SAAOP Status 🖨		AO 🖨	OECD Status 🖨	OECD Project
			Clear ~	Clear ~			Clear ~	
458	AhR activation in the liver leading to Subsequent Adverse Neurodevelopmental Outcomes in Mammals	Prakash Patel	Under development: Not open for comment. Do not cite					
27	Cholestatic Liver Injury induced by Inhibition of the Bile Salt Export Pump (ABCB11)	Mathieu Vinken	Under development: Not open for comment. Do not cite	Included in OECD Work Plan	<ul> <li>Inhibition, Bile Salt Export Pump (ABCB11)</li> </ul>	Cholestasis, Pathology	Under Developme nt	1.19
220	Cyp2E1 Activation Leading to Liver Cancer	Francina Webster	Open for citation & comment	Included in OECD Work Plan	<ul> <li>Activation of Cyp2E1</li> </ul>	Liver Cancer	WPHA/WN T Endorsed	1.24
240	DNA Adducts Leading to Liver Hemangiosarcoma	Annie Jarabek	Under development: Not open for comment. Do not cite	Under Development				
144	Endocytic lysosomal uptake leading to liver fibrosis	Marina Kuburic	Under development: Not open for comment. Do not cite	Included in OECD Work Plan	<ul> <li>Endocytotic lysosomal uptake</li> </ul>	N/A, Liver fibrosis	EAGMST Under Review	1.47
278	IKK complex inhibition leading to liver injury	Nanette Vrijenhoek	Under development: Not open for		<ul> <li>Inhibition, IKK complex</li> </ul>	<ul><li>Necrotic Tissue</li><li>Liver Injury</li></ul>		

#### <u>Adverse Outcome Pathways</u> (AOPs)



#### objectives <sup>-</sup>

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## The Integrated Testing Strategy (ITS)

#### Définition

- method integrating hazard assessment information from several sources
- built with the 3Rs principle in mind
- allows the evaluator to determine the need for additional testing

#### **Objectives**

- Promote the use of data from alternative methods and reduce the need for animal testing
- Use integrated approaches to testing and evaluation (IATA) (set of data collection, testing and evaluation methods integrating data from different levels: in vitro, in vivo, in chemico, in silico, physicochemical)

(IATA : <u>I</u>ntegrated <u>A</u>pproches on **T**esting and **A**ssessment)



## Allergic contact dermatitis: a type IV hypersensitivity reaction



d'après Saint-Mezard et al., Eur. J. Dermatol. (2004).

AOP (OECD) ????

#### AOP (OECD)

#### ????





d'après Kimber et al., Tox. Sciences (2011)

#### AOP of skin sensitization



#### AOP of skin sensitization: alternatives methods



#### AOP of skin sensitization: alternatives methods





E. Clouet, S. Kerdine-Römer, PJ. Ferret. Toxicology in Vitro, 45 (2017): 374-385

Selected test sequence



#### ..... what we have proposed

#### How to integrate all the KEs of the AOP into a single tool?



#### **KE1** : Initial events



#### KE2 : Nrf2 pathway and gene expression



d'après Chen et al., Diabetes Metab J. (2014)

#### KE2: Nrf2 pathway and gene expression

a.





b.

## KE3 : Modulation of THP-1 phenotype





Cell surface markers CD54/CD86 ? Modulation of the response by inflammatory cytokines?

#### KE3 : Modulation of THP-1 phenotype



## **KE4** : Proliferation of LT



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			Key 1		Key 2						Key	3				Key 4
		C re	hemical activity	Proteins activity	DNA-binding ELISA	Gei	nes expres on THP-1 (SENS-IS	sion l )	Sur mar	face kers	Modulation by inflammatory cytokines	Cytoki	nes q	uantifi	cation	CD4⁺ T cell proliferation
		ROS	GSH depletion	Western blot	Nrf2 TransAM	IRR	SENS-IS	ARE	CD <sub>54</sub>	CD <sub>86</sub>	Cytokine array	CCL4	IL-8	IL-16	IL-18	
	PBS					7	1	2			IL1-ra MIF					
SITIZERS	DMSO					6	2	2			IL1-ra MIF IL-16-/+ CCL5/RANTES					
N SEN	BZK					14	4	7			IL-16++ CCL5/RANTES					
ON	t-BHQ					11	1	11			IL-16++ CCL5/RANTES+					
IRR	SDS					13	7	5			IL-16++ CCL5/RANTES					
AK	RESO					16	4	12			IL-8+ IL-16+ CCL5/RANTES+					
WEA	EUG					12	2	10			IL-8 IL-16-/+ CCL5/RANTES					
(r)	FAR					9	8	7			IL-8+ IL-16++ IL-18 CCL5/RANTES+					
IODERATI	GER					7	4	4			IL-8++ IL-16++ CCL5/RANTES+					
4	CinA					18	6	13			IL-16 IL-8+ IL-18+					
STRONG	MIT					17	7	11			IL-16+ IL-8 +++ IL-18++					

#### CONCLUSION



## CONCLUSION





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# The THP-1 cell toolbox: a new concept integrating the key events of skin sensitization

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