



# Holistic Approach to Human Risk Assessment- Is the Current Approach Fit for Purpose?

**EFSA Scientific Conference 2018**

Susanne Hougaard Bennekou  
Senior Advisor, The Danish EPA  
Parma, 19th. September 2018

# Disclaimer

**The opinions expressed in this presentation are the author's own and do not reflect the view of the Danish EPA**



# **Holistic Approach**

## **Current Approach Fit for Purpose?**

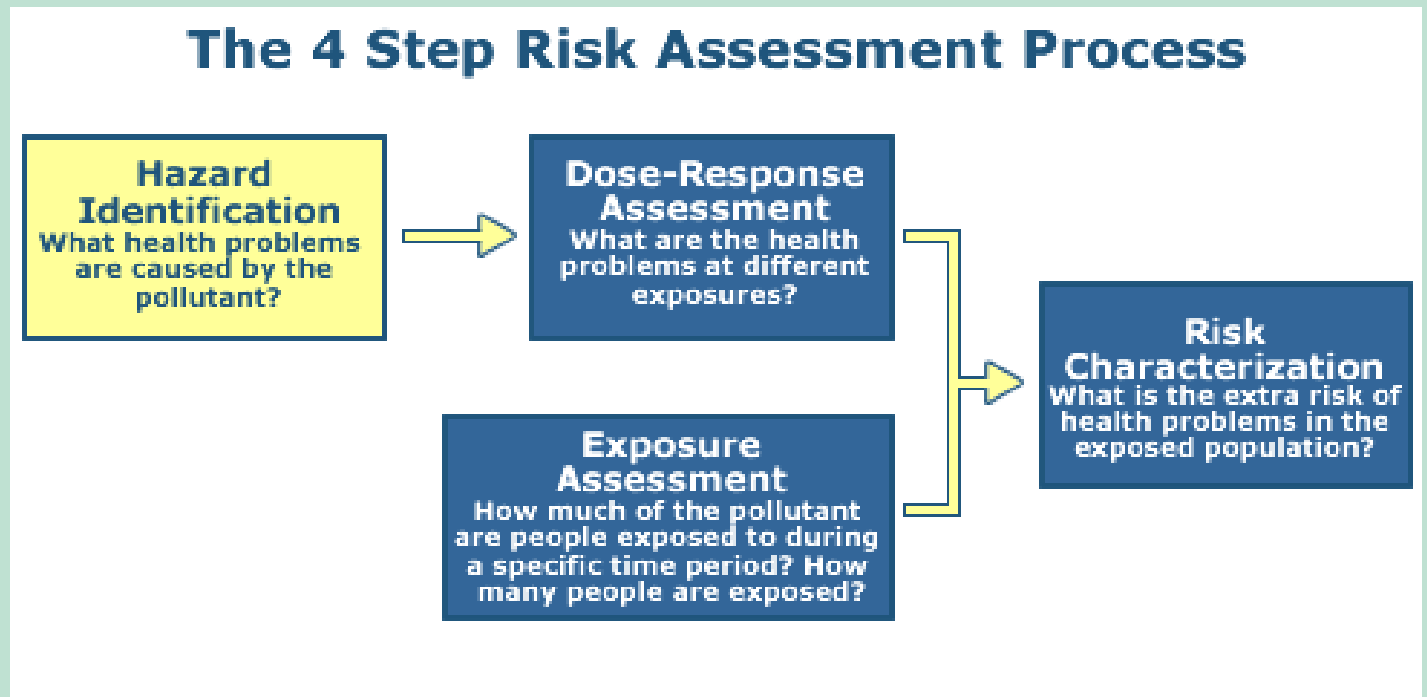
**Is it good enough at what it is meant to do?**

**Do regulations support a holistic approach?**

**?**

**Compartmentalised?**

# Compartments



## Single Substance Evaluation

Cmpd 1  
Cmpd 4

Cmpd 2  
Cmpd 4

Cmpd 3  
Cmpd $\infty$

## Regulatory Siloes

REACH

Pesticide

Biocides

Medicines

## Geographical

Countries

Unions

Continents



# Holistic Approach?

**Do we need it ?**



**Transparency**  
**&**  
**Trust** - Informed Skepticism  
**In**  
**Safety**  
**Assessment**



## Data requirement - active substance

Toxicokinetics – absorption, distribution, excretion, metabolism –single and repeated dose **rat**

Acute exposure - oral, dermal, inhalation **rat**

Irritation – eye, skin **rabbit**

Sensitisation **mouse**

Subchronic toxicity (28-90 days ) **rat**

Subchronic toxicity (28 days – 1 year) **dog**

Genotoxicity – in vitro (mutagenicity, chromosome aberrations, aneugenicity)

Genotoxicity – in vivo (chromosome aberrations – possibly others) **mice**

Chronic toxicity (2 year) **rats**

Carcinogenicity (2 year) **rats**

Carcinogenicity **mice**

Teratogenicity **rat**

Teratogenicity **rabbit**

Reproduction – 1 or 2 generations **rat**

Neurotoxicity (acute and/or chronic exposure) **rat**, Developmental neurotoxicity **rat**

**All** relevant data from open litteratur (systematic review)

Others – special studies on endocrine end points

# Confidence in the risk assessment?

## Active Substance

- Wide range test
- Regulate on the basis of no observed adverse effect levels
- Reference values should cover vulnerable groups

## Exposure

- Reasonable upper limits are estimated for the levels of human exposure to the active substance

## Risk Assessment

- Consumers
- Operator
- Worker
- Bystander
- Resident



**Confidence in the risk assessment?**

**Yes**

**But how Safe**



# Tough ?

- Relies heavily on non-human data
- Relies on in vivo data – not designed to provide mechanistic understanding
- Multi-factorial disease etiologies not covered
- Co-exposures not considered
- Reference doses based on NOAELs – does not allow quantification of the uncertainty
- Deterministic reference doses – coverage and uncertainty is not determined
- Protection Goal is not well-defined

**Protection Goal**

**Risk Metric**

**DEFINE**

**“ENSURE NOT ANY HARMFUL EFFECT”**

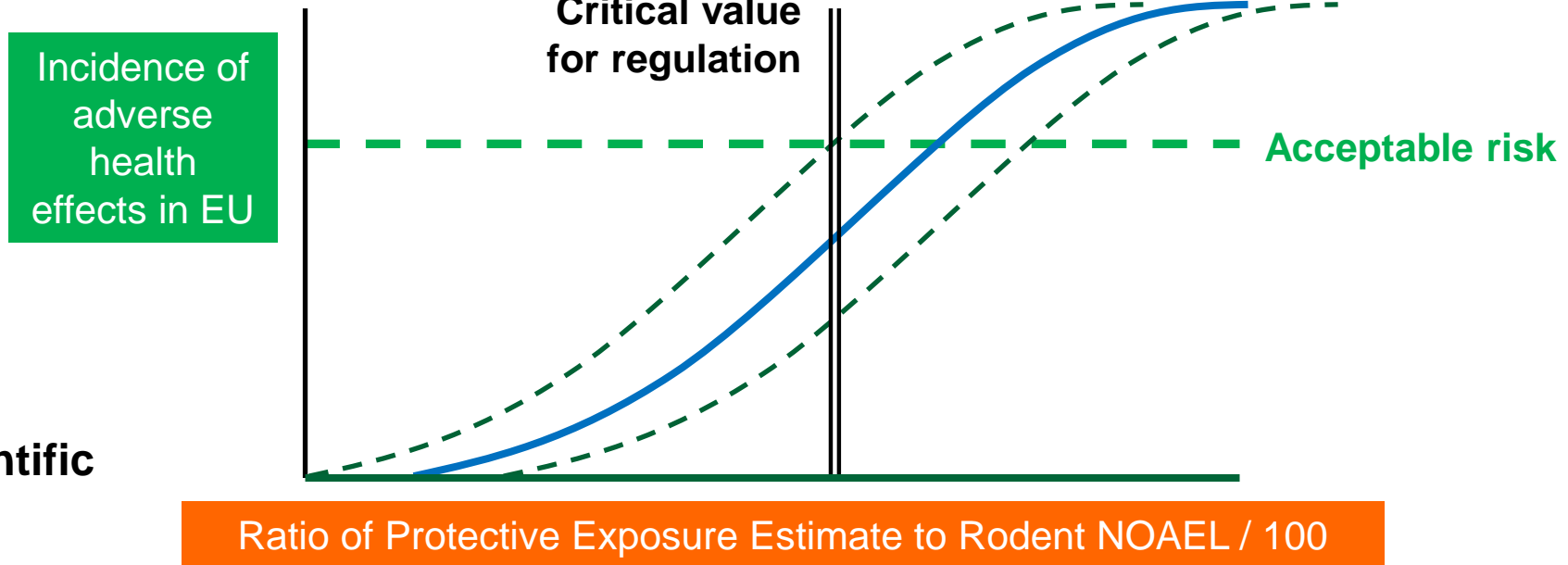


**NO ADVERSE EFFECT LEVEL IN RODENTS / 100**  
**CONSERVATIVE ESTIMATE OF EXPOSURE**

**ASSESS**

*Pesticide Reg. 107/2009*

**CALIBRATE**



**EFSA Guidance on Uncertainty in Scientific Assessment**



*Courtesy of Andy Hart*

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# PRESCRIPTIVE

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**What do we prescribe ?**

**Bad prescription**

**Poor reproducibility**

**Difficult to interpretate**

**Inefficient**

**Expensive**

**Insensitive**

**Relevance**



# Are there nasty surprises?

Ntzani EE, Chondrogiorgi M,  
Ntritsos G, Evangelou E, Tzoulaki I

EFSA supporting publication 2013:EN-497

## EXTERNAL SCIENTIFIC REPORT

### Literature review on epidemiological studies linking exposure to pesticides and health effects<sup>1</sup>

Evangelia E Ntzani, Chondrogiorgi M, Ntritsos G, Evangelou E, Tzoulaki I

Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, Greece

602 epidemiological studies - >6000 data analysis

In meta-analysis consistent increased risk

- **Parkinson's Disease**
- **Childhood Leukemia**
- Type II diabetes
- Asthma
- Amyotrophic lateral sclerosis
- Some cancer types – liver, breast, stomach

**Do not allow conclusions but still concern**  
**What is the biological plausibility?**



ADOPTED: 14 December 2016

doi: 10.2903/j.efsa.2017.4691

# **Investigation into experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia<sup>1</sup>**

EFSA Panel on Plant Protection Products and their residues (PPR),  
Colin Ockleford, Paulien Adriaanse, Philippe Berny, Theodorus Brock, Sabine Duquesne,  
Sandro Grilli, Antonio F Hernandez-Jerez, Susanne Hougaard Bennekou, Michael Klein,  
Thomas Kuhl, Ryszard Laskowski, Kyriaki Machera, Olavi Pelkonen, Silvia Pieper, Rob Smith,  
Michael Stemmer, Ingvar Sundh, Ivana Teodorovic, Aldrik Tiktak, Chris J Topping,  
Gerrit Wolterink, Karine Angeli, Ellen Fritsche, Antonio F Hernandez-Jerez, Marcel Leist,  
Alberto Mantovani, Pablo Menendez, Olavi Pelkonen, Anna Price, Barbara Viviani,  
Arianna Chiusolo, Federica Ruffo, Andrea Terron and Susanne Hougaard Bennekou

# PRESCRIPTIVE ?

**Strengths: We get a lot of data - FOMO**

**Weakness: Not always** (or even necessary) **relevant data**

**Opportunity: FODU - Fully Optimise Data Use**

**Challenge: Utilize new developments in science**



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**PRESCRIPTIVE**

**FLEXIBLE**

# FODU

Endpoint	Cmpd 1	Cmpd 2	Cmpd 3	Cmpd 4	Metb. 1	Metb. 2	Metb. 2
Similar toxophore	+	+	+	+	+	+	+
Kinetics	+	+	+	+	-	-	-
Genotoxicity	+	+	+	+	+	+	+
Repeat-dose toxicity	+	+	+	+	+	+	-
Carcinogenicity	+	+	+	+	-	-	-
Teratogenicity	+	+	+	+	+	-	-
Reproductive toxicity	+	+	(+)	+	+	-	-
ED activity	+	(+)	(+)	+	+	-	-
Neurotoxicity	+	+	+	+	-	-	-
DNT	--	+	-	-	-	-	-

2018

2008

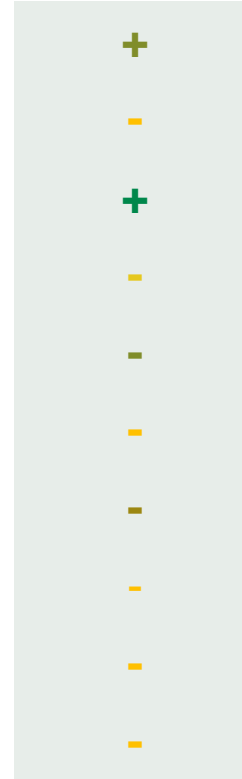
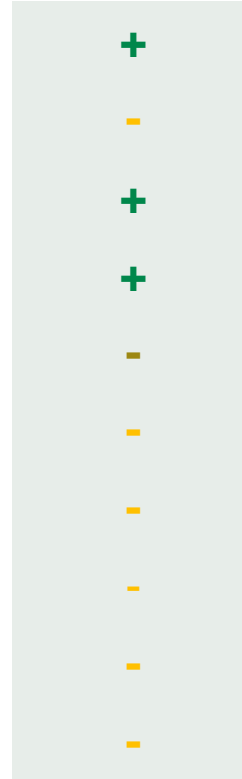
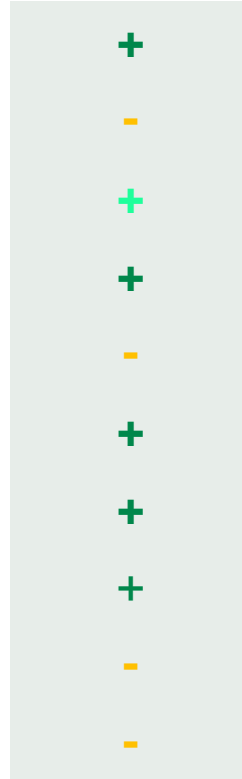
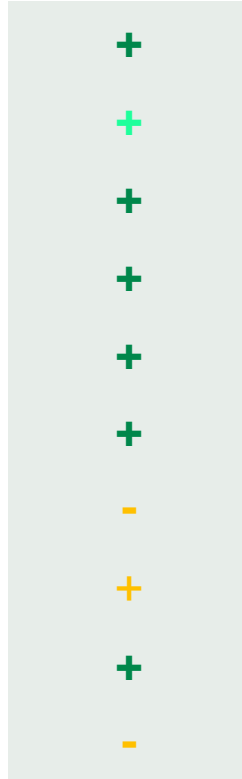
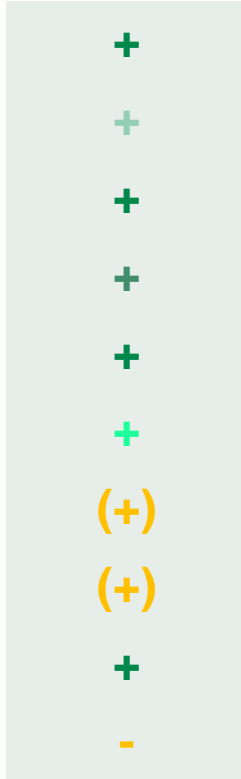
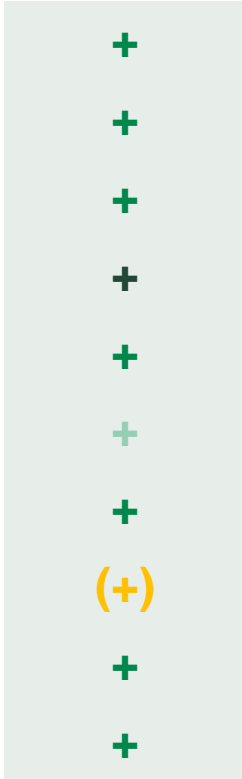
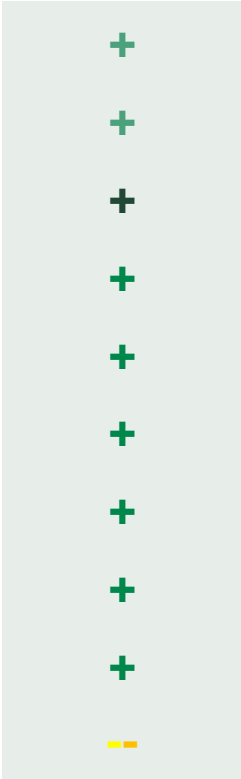
2005

2011

2013


























































































2013

2005



# FODU

## Read-Across

						
				-	-	-
						
						-
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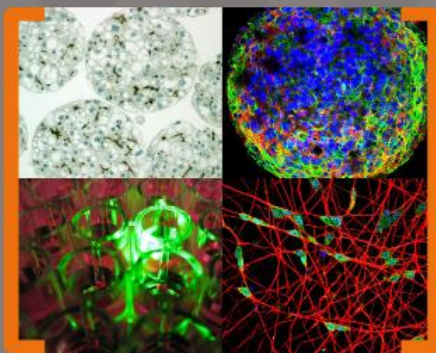
An Integrated **EU**ropean ‘Flagship’ Program  
Driving Mechanism-based **Toxicity** Testing and  
**Risk** Assessment for the 21<sup>st</sup> Century

Mechanism-based test methods in testing batteries for:

- Pragmatic, solid “read across” procedures
- Ab initio hazard and risk assessment strategies

Based on

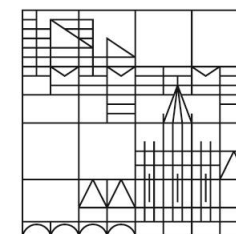
1. Combination of in silico and in vitro assays
2. Systems toxicology/biology, AOPs
3. Test system evaluations
4. Risk assessment and uncertainties



<http://www.eu-toxrisk.eu/>



Universität  
Konstanz



JOHNS HOPKINS  
BLOOMBERG SCHOOL  
OF PUBLIC HEALTH

“Internationalisation of read across as validated new approach  
method (NAM) for regulatory toxicology “

*ALTEX* 2016 ; 33(2): 149–166. doi:10.14573/altex.1601251.

t<sup>4</sup> report\*: Toward Good Read-Across Practice (GRAP) Guidance

Nicholas Ball<sup>1,§</sup>, Mark T. D. Cronin<sup>2,§</sup>, Jie Shen<sup>3,§</sup>, Karen Blackburn<sup>4</sup>, Ewan D. Booth<sup>5</sup>, Mounir Bouhifd<sup>6</sup>, Elizabeth Donley<sup>7</sup>, Laura Egnash<sup>7</sup>, Charles Hastings<sup>8</sup>, Daland R. Juberg<sup>1</sup>, Andre Kleensang<sup>6</sup>, Nicole Kleinstreuer<sup>9</sup>, E. Dinant Kroese<sup>10</sup>, Adam C. Lee<sup>11</sup>, Thomas Luechtefeld<sup>6</sup>, Alexandra Maertens<sup>6</sup>, Sue Marty<sup>1</sup>, Jorge M. Naciff<sup>4</sup>, Jessica Palmer<sup>7</sup>, David Pamies<sup>6</sup>, Mike Penman<sup>12</sup>, Andrea-Nicole Richarz<sup>2</sup>, Daniel P. Russo<sup>13</sup>, Sharon B. Stuard<sup>4</sup>, Grace Patlewicz<sup>14</sup>, Bennard van Ravenzwaay<sup>10</sup>, Shengde Wu<sup>4</sup>, Hao Zhu<sup>13</sup>, and Thomas Hartung<sup>6,15</sup>



**SOT** | Society of  
Toxicology  
www.toxsci.oxfordjournals.org



TOXICOLOGICAL SCIENCES, 165(1), 2018, 198–212

doi: 10.1093/toxsci/kfy152

Advance Access Publication Date: July 11, 2018

Research Article

# Machine Learning of Toxicological Big Data Enables Read-Across Structure Activity Relationships (RASAR) Outperforming Animal Test Reproducibility

Thomas Luechtefeld,<sup>\*,†</sup> Dan Marsh,<sup>†</sup> Craig Rowlands,<sup>‡</sup> and Thomas Hartung<sup>\*,§,1</sup>

<sup>\*</sup>Johns Hopkins University, Bloomberg School of Public Health, Center for Alternatives to Animal Testing (CAAT), Baltimore, Maryland 21205; <sup>†</sup>ToxTrack, Baltimore, Maryland 21209; <sup>‡</sup>UL Product Supply Chain Intelligence, Underwriters Laboratories (UL), Northbrook, Illinois 60062; and <sup>§</sup>University of Konstanz, CAAT-Europe, Konstanz 78464, Germany





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LAST NEWS

March 2014  
eTOX Newsletter

Issue Number 30 of the eTOX Newsletter has been released in March.

March 2014  
eTOX at SOT 2014

eTOX will present 3 posters at the 53rd Annual Meeting of the Society of Toxicology.

[+ info]

Welcome to the eTOX Website

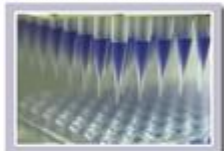
Objectives

The eTOX project aims to develop a drug safety database from the pharmaceutical industry legacy toxicology reports and public toxicology data; innovative in silico strategies and novel software tools to better predict the toxicological profiles of small molecules in early stages of the drug development pipeline

Funding

eTOX, under Grant Agreement #115002, is funded by the Innovative Medicines Initiative Joint Undertaking (IMI-JU), a unique partnership between the European Community and the European Federation of Pharmaceutical Industries and Associations (EFPIA).

eTOX Roadmap



- The Project
- The Consortium
- News
- Results
- Related Projects
- Intranet

The eTRANSAFE (Enhancing TRANslational SAFETY Assessment through Integrative Knowledge Management) project works to improve the efficiency of translational safety assessment approaches during the medicines discovery pipeline











# Comprehensive analysis of correspondence and validity of animal data for human safety

CONTINUE READING





# Read Across

Regulation	Read Across
Food Contact Materials	
Feed	
Flavourings	
Biocides	
REACH	
Pesticide Regulation	
Pesticide: Data Requirements	
Pesticides: Identification of Endocrine Disruptors	



## Amendment to 1107/2009 on placing of Plant Protection Products on the market - on the identification of ED's

1. it shows an **adverse effect** in an **intact organism** or its progeny, which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in the susceptibility to other influence;
2. it has an endocrine **mode of action**, i.e. alters the function(s) of the endocrine system;
3. the adverse effect is a **consequence** of the endocrine mode of action

**Guidance for the identification of endocrine  
disruptors in the context of Regulations (EU) No  
528/2012 and (EC) No 1107/2009**

Draft

For consultation of the ECHA and EFSA Scientific Bodies (ECHA Biocidal Products Committee, EFSA Scientific Committee and PPR Panel, and the EFSA Pesticides Steering Network)

Drafted by EFSA and ECHA staff, with support from JRC  
16 April 2018

## Conceptual Framework for testing and assess endocrine disrupters

### Mammalian and non-mammalian Toxicology

#### Level 1

Existing Data and Non-Test Information

#### Level 2

*In vitro* assays providing data about selected endocrine mechanism(s) / pathway(s)

#### Mammalian Toxicology

#### Non-mammalian Toxicology

#### Level 3

*In vivo* assays providing data about selected endocrine mechanism(s) / pathway(s)

#### Level 4

*In vivo* assays providing data on adverse effects on endocrine relevant endpoints

#### Level 5

*In vivo* assays providing more comprehensive data on adverse effects on endocrine relevant endpoints over more extensive parts of the life cycle of the organism

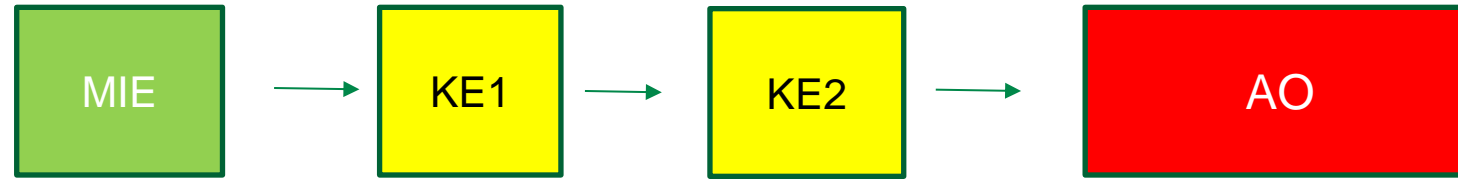
14 · OECD WORK ON ENDOCRINE DISRUPTING CHEMICALS



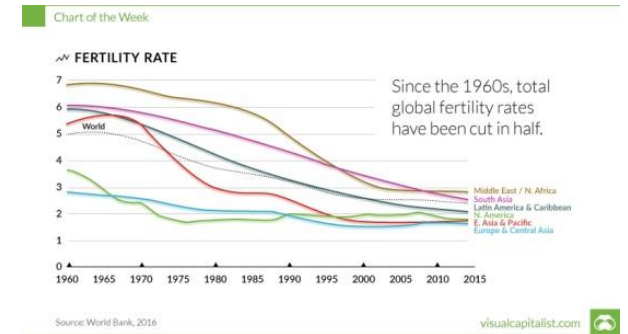
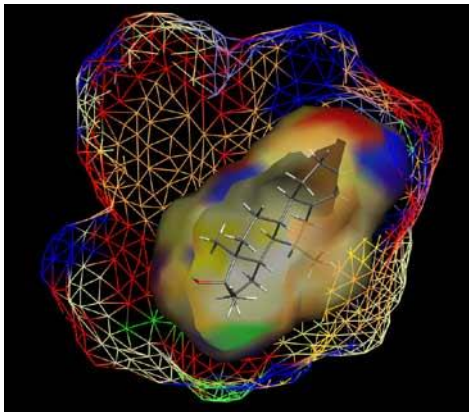
Endpoint	Cmpd 1	Cmpd 2	Cmpd 3
Acute toxicity	+	+	+
Kinetics	+	+	+
Genotoxicity	+	+	+
<b>Repeat-dose toxicity</b>	+	+	+
<b>Carcinogenicity</b>	+	+	+
<b>Teratogenicity</b>	+	+	+
<b>Reproductive toxicity</b>	+	+	+
<b>ED activity</b>			
Androgen	+	+	+
Estrogen	+	+	+
Thyroid	+	+	+
Steroidgenesis	+	+	+
Neurotoxicity	+	+	+
DNT	--	+	-

Endpoint	Cmpd 1	Cmpd 2	Cmpd 3	Cmpd 4
Acute toxicity	+	+	+	+
Kinetics	+	+	+	+
Genotoxicity	+	+	+	+
<b>Repeat-dose toxicity</b>	+	+	+	+
<b>Carcinogenicity</b>	+	+	+	+
<b>Teratogenicity</b>	+	+	+	+
<b>Reproductive toxicity</b>				<b>?</b>
<b>Anogenital distance</b>	↓	↓	↓	<b>?</b>
<b>ED activity</b>				<b>?</b>
Androgen	↓	↓	↓	↓
Estrogen	n.a.	n.a.	n.a.	n.a.
Thyroid	n.a.	n.a.	n.a.	n.a.
Steroidogenesis	n.a.	n.a.	n.a.	n.a.
Neurotoxicity	+	+	+	+
DNT	--	+	-	-

# Adverse Outcome Pathway



## Androgen receptor antagonism leads to impairment of reproductive capacity



# OECD AOP Status 18th September 2018

AOP	Modality	Status
Aromatase Inhibition leading to reproductive dysfunction	s	Endorsed
Androgen receptor agonism leading to reproductive dysfunction	A	Approved
Aromatase (Cyp19a1) reduction leading to impaired fertility in adult female	S	Under review
Estrogen receptor antagonism leading to reproductive dysfunction	E	Under review
Inhibition of Thyroperoxidase and Subsequent Adverse Neurodevelopmental Outcomes in Mammals	T	Under review
PPAR $\alpha$ activation in utero leading to impaired fertility in males	other	Under review
Inhibition of Na <sup>+</sup> /I <sup>-</sup> symporter (NIS) leads to learning and memory impairment	T	Under development Open for comments
A lot under development Very different level of matureness		Not OECD workplan

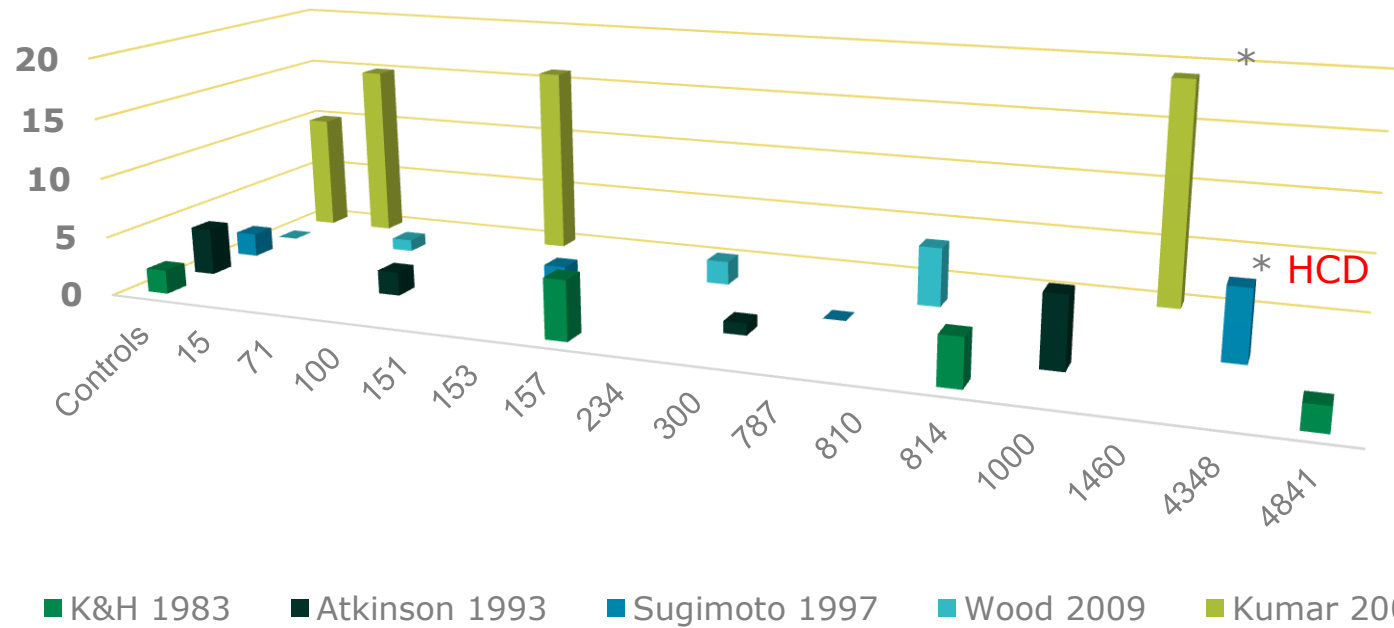


# C&L

## Classification & Labelling



## Malignant lymphomas in male mice



*Courtesy of Danielle Cours Marques*

# Should we care ?

# Metsulfuron-methyl

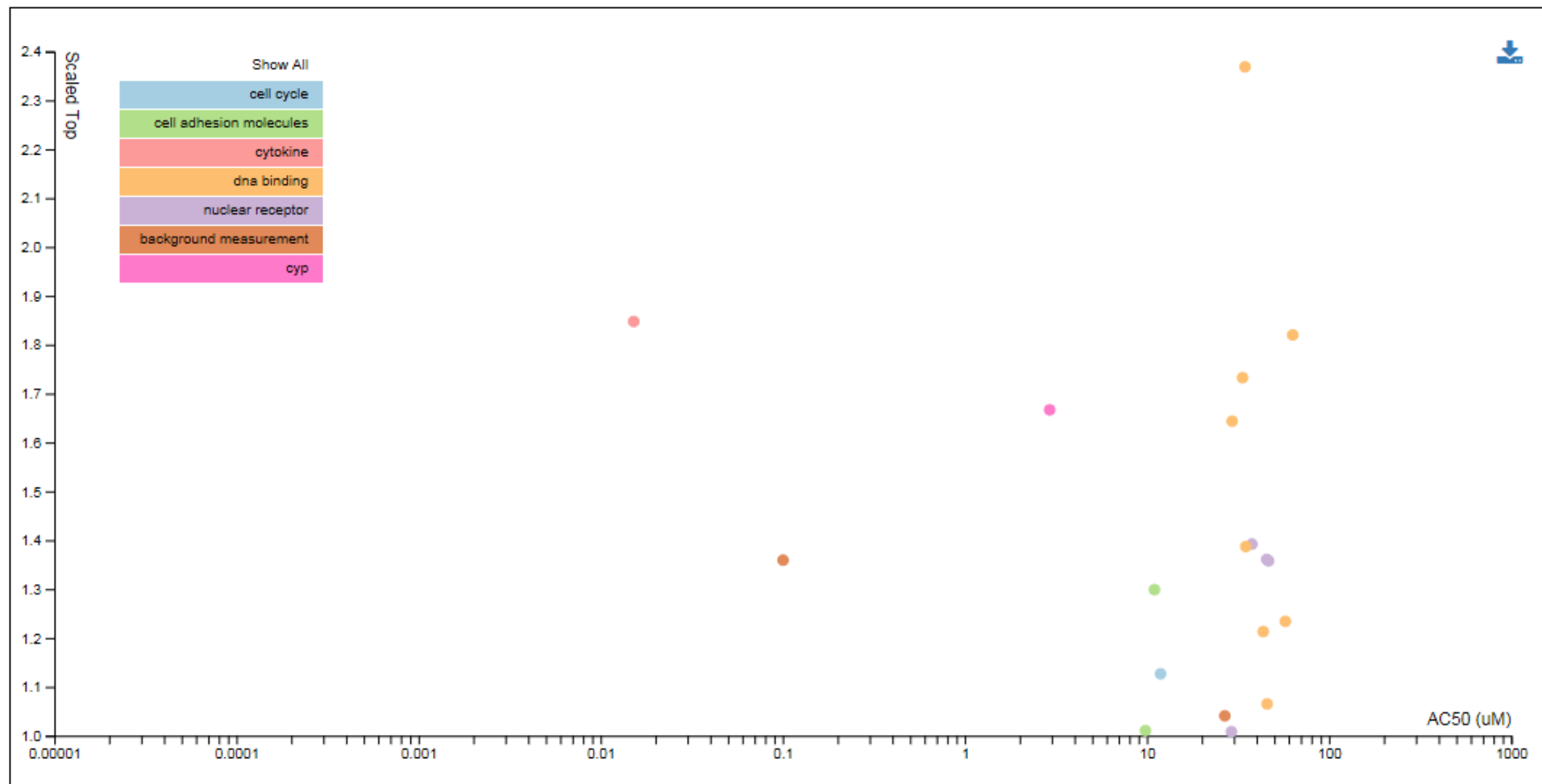
74223-64-6 | DTXSID6023864

Searched by DSSTox Substance Id.

- DETAILS
- EXECUTIVE SUMMARY
- PROPERTIES
- ENV. FATE/TRANSPORT
- HAZARD
- ▶ ADME
- ▶ EXPOSURE
- ▼ **BIOACTIVITY**
  - TOXCAST: SUMMARY**
  - PUBCHEM
  - TOXCAST: DATA
  - TOXCAST: MODELS
- SIMILAR COMPOUNDS
- GENRA (BETA)
- RELATED SUBSTANCES
- SYNONYMS

## Chemical Activity Summary i

### i TOXCAST DATA



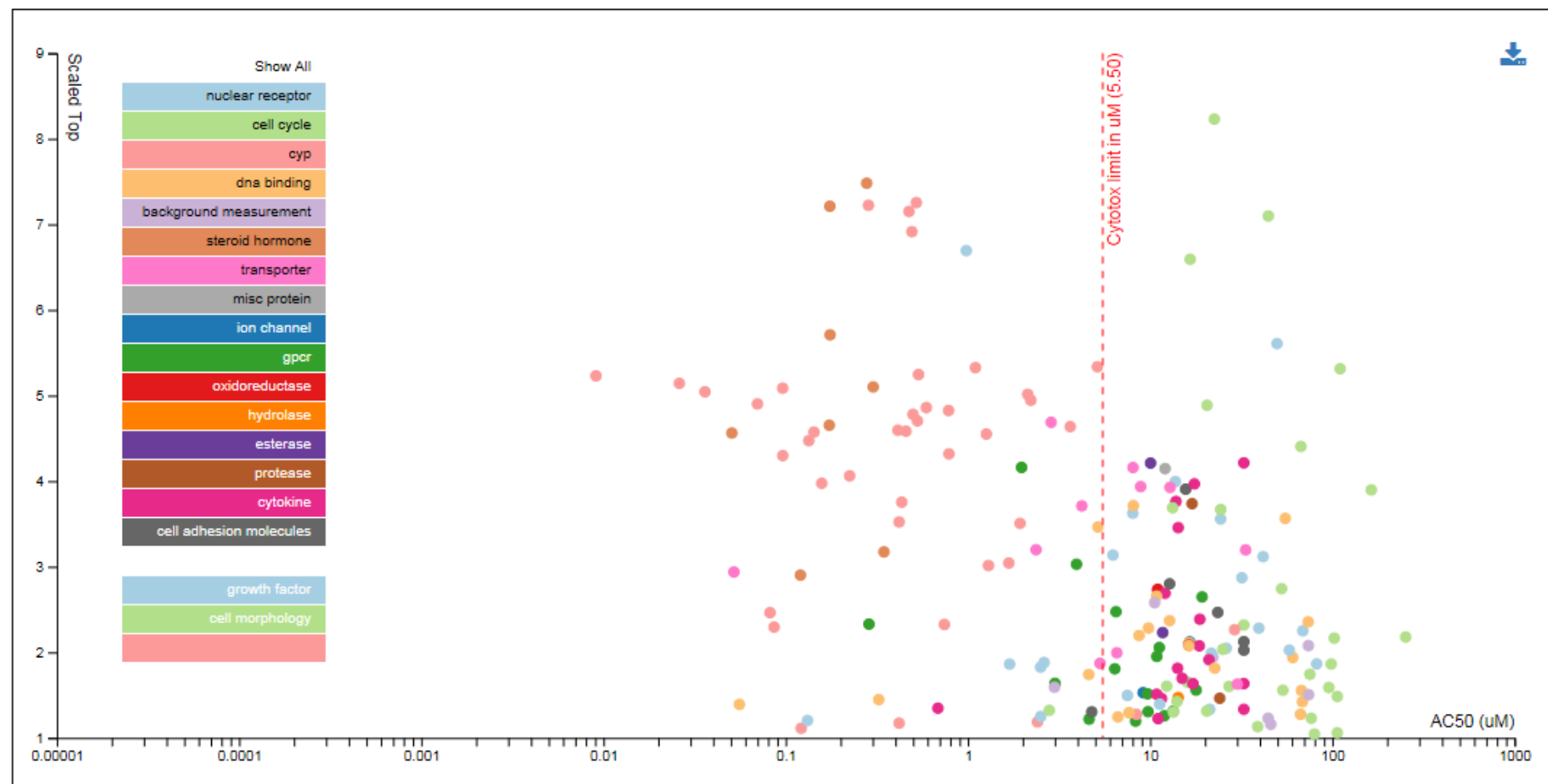
# Prochloraz

67747-09-5 | DTXSID4024270

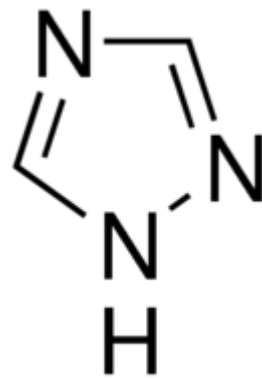
Searched by DSSTox Substance Id.

## Chemical Activity Summary i

### i TOXCAST DATA



- DETAILS
- EXECUTIVE SUMMARY
- PROPERTIES
- ENV. FATE/TRANSPORT
- HAZARD
- ▶ ADME
- ▶ EXPOSURE
- ▼ **BIOACTIVITY**
  - TOXCAST: SUMMARY**
  - PUBCHEM
  - TOXCAST: DATA
  - TOXCAST: MODELS
- SIMILAR COMPOUNDS
- GENRA (BETA)
- RELATED SUBSTANCES
- SYNONYMS
- ▶ LITERATURE

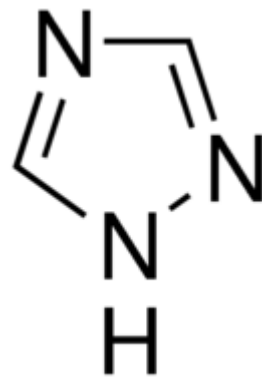


1,2,4 Triazole

Toxic to reproduction  
Endocrine disruptive activity?  
Developmental neurotoxicity?  
Carcinogenicity?

**Sources:**

Cyproconazole, Difenoconazole, Metconazole, Myclobutanil, Propiconazole, Prothioconazole, Triadimenol, Triticonazole, Epoxiconazole, Fenbuconazole, Paclobutrazol, Penconazole, Tebuconazole  
Tetraconazole



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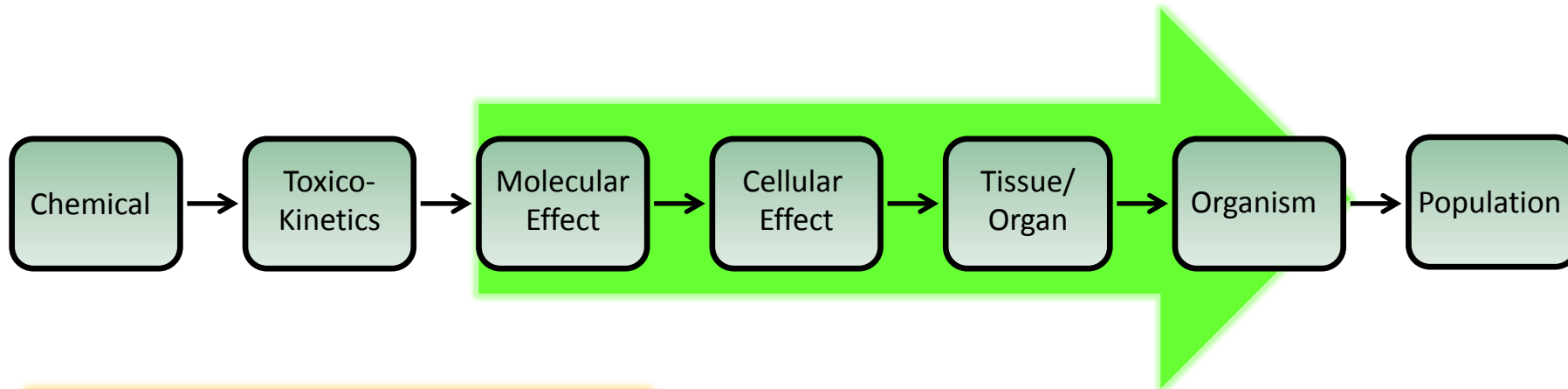
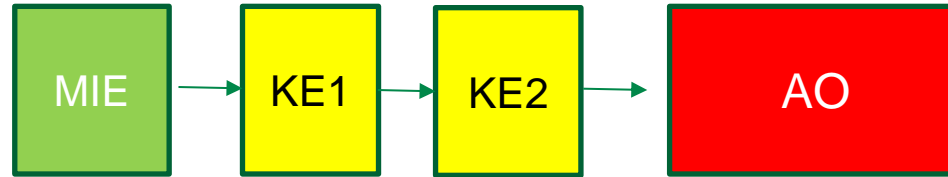
**Sources:**

**Cyproconazole**, Difenoconazole, Metconazole, Myclobutanil, Propiconazole, Prothioconazole, Triadimenol, Triticonazole, Epoxiconazole, Fenbuconazole, Paclobutrazol, Penconazole, **Tebuconazole**  
Tetraconazole

**Other sources?**  
**De-nitrification**



# Adverse Outcome Pathway



QSAR, Modeling, Exposure & TK

In Vitro

In Vivo

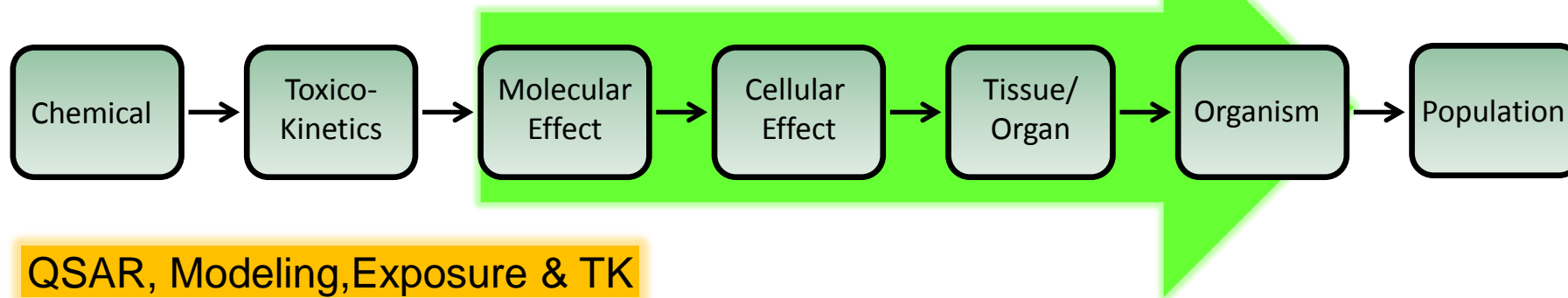
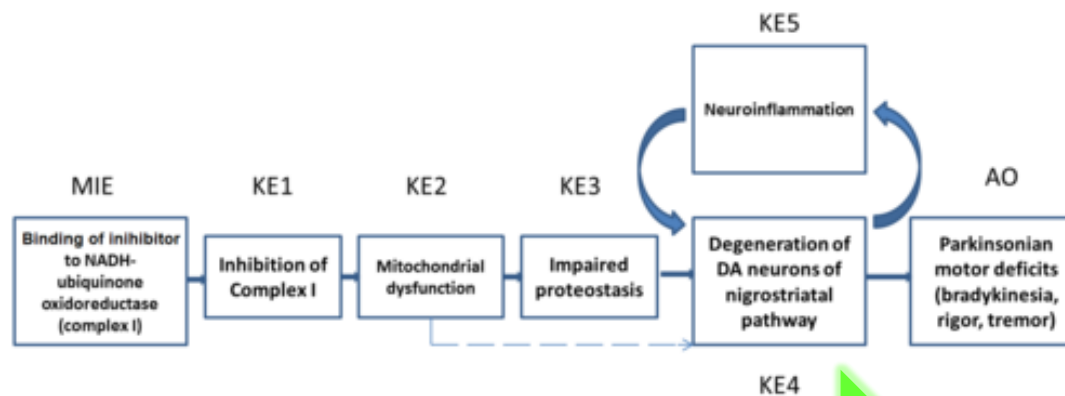
Biomonitoring

Epidemiological



# Inhibition of the mitochondrial complex I of nigrostriatal neurons leads to parkinsonian motor deficits

AOPwiki #3



QSAR, Modeling, Exposure & TK

In Vitro

In Vivo

Biomonitoring

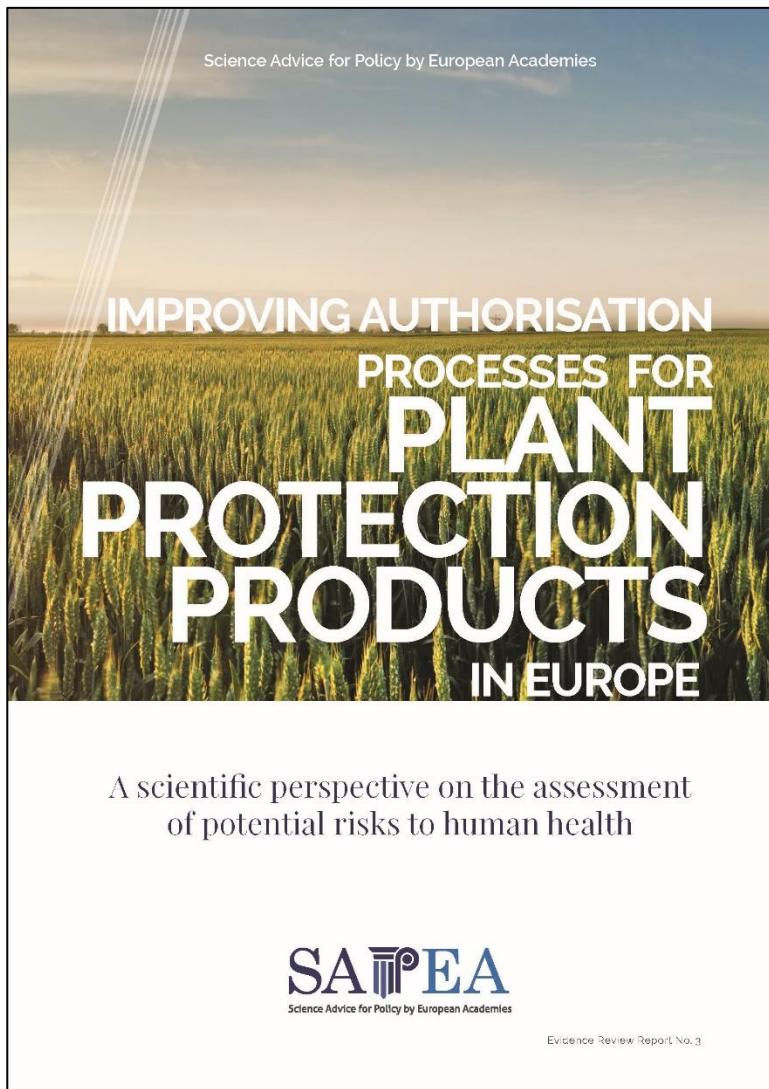
Epidemiological



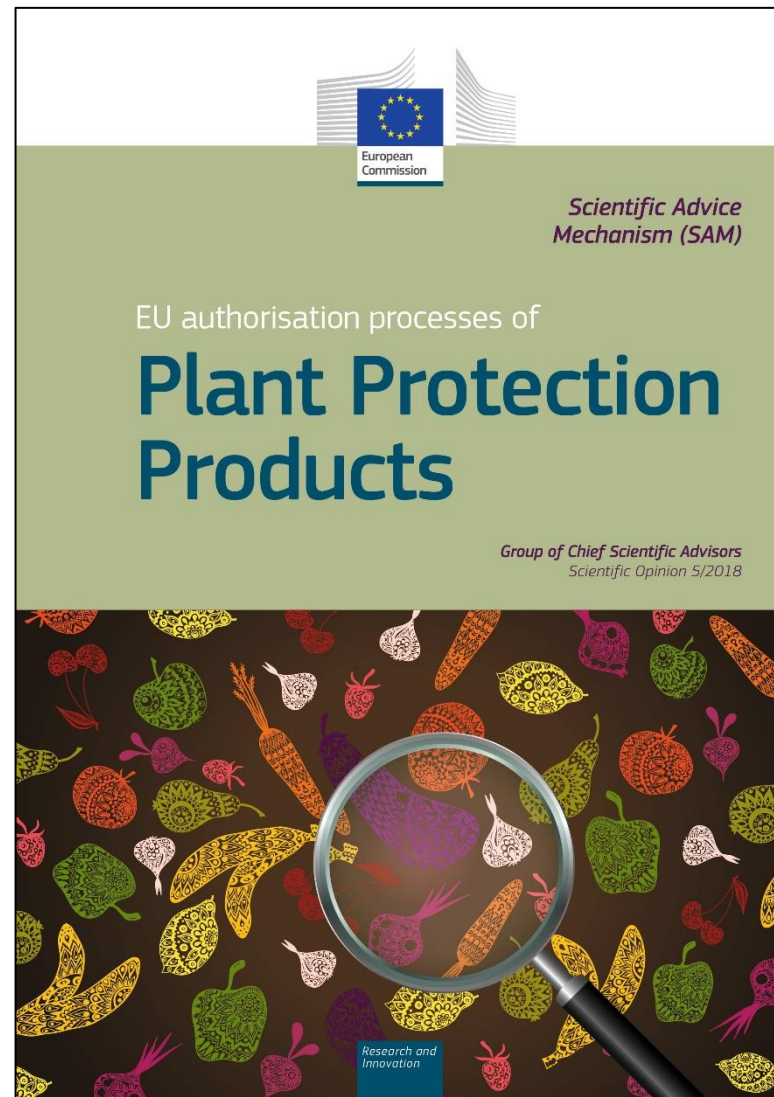


# *Holistic Wish List*

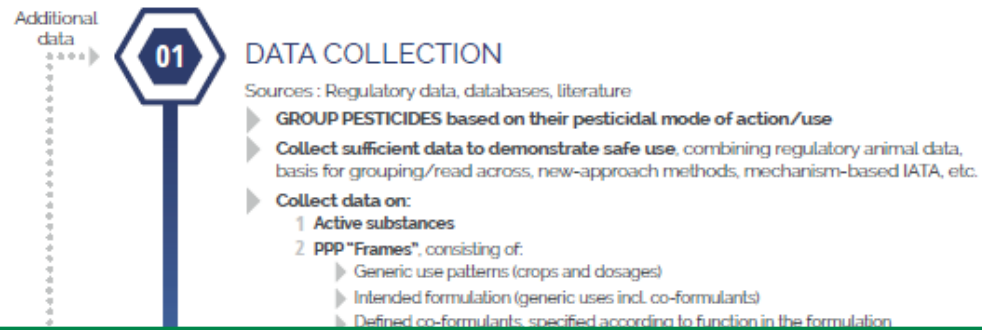
- **Screening**
- **AOPs**
- **Data availability**
- **Define Protection Goals**
- **Rigorous analysis of uncertainties**
- **Flexible data requirements**
- **Harmonised Approaches**



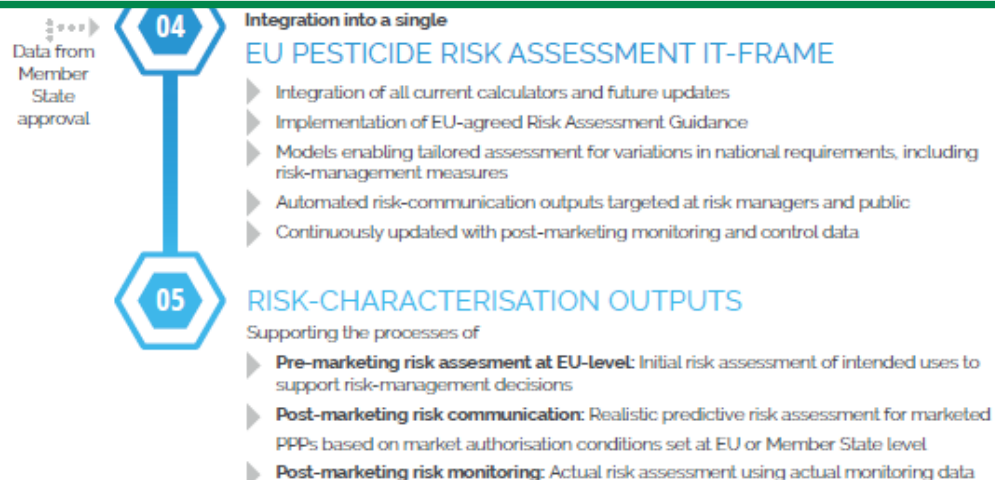
[www.sapea.info/plantprotectionproducts](http://www.sapea.info/plantprotectionproducts)



<https://ec.europa.eu/research/sam/index.cfm?pg=pesticides>



- Efficient use of expert knowledge resources and data
- Agile in regard to incorporating new science and data into risk assessment
- Support risk management decisions and provide transparency to the public
- Address co-formulants in PPPs
- Address risk assessment for mixtures and candidates for substitution
- Integrate post-marketing data (monitoring) into risk assessment
- Support a harmonised system







# Thanks

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