



JRC EURL ECVAM Activities on Combined Exposure to Multiple Chemicals

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JRC F3 Chemical Safety and Alternative Methods

Communication on Chemical Mixtures 2012 and Chemical Strategy for Sustainability 2020

2012

- Review of new evidence since 2009 SoA report on mixtures
- Filling gaps identified

2020



EUROPEAN COMMISSION

Brussels, 31.5.2012
COM(2012) 252 final

COMMUNICATION FROM THE COMMISSION TO THE COUNCIL

The combination effects of chemicals

Chemical mixtures

COMMISSION STAFF WORKING DOCUMENT

Progress report on the assessment and management of combined exposures to multiple chemicals (chemical mixtures) and associated risks

Accompanying the document

COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS

**Chemicals Strategy for Sustainability
Towards a Toxic-Free Environment**

{COM(2020) 667 final} - {SWD(2020) 225 final} - {SWD(2020) 247 final} -
{SWD(2020) 248 final} - {SWD(2020) 249 final} - {SWD(2020) 251 final}

Review of State of the Art

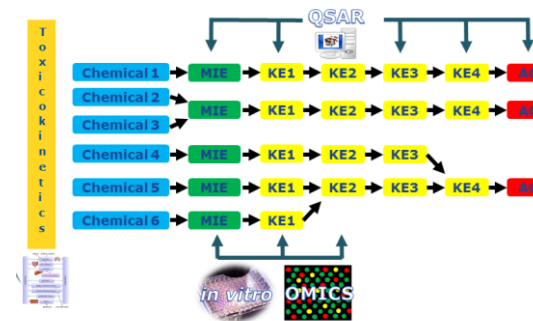
Regulatory Requirements

Kienzler et al 2014
Kienzler et al 2016



Review of case studies

Bopp et al 2016



Scientific Methodologies and current practices

Bopp et al 2015
Desalegn et al 2019
Kienzler et al 2019
Pletz et al 2020
Pistollato et al 2020, 2021

Scientific Advances and policy needs

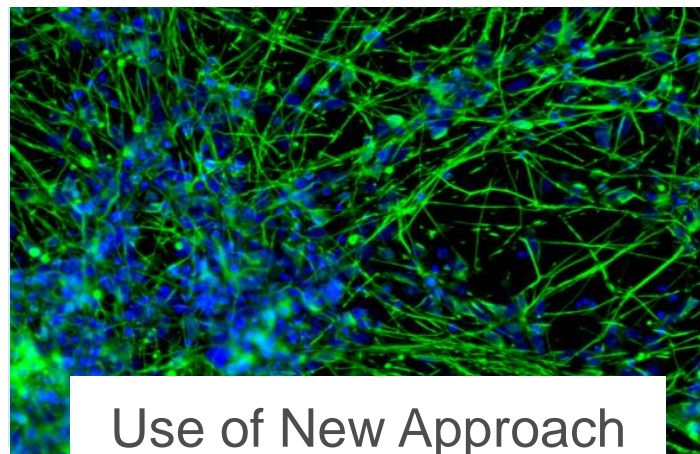
Bopp et al 2018
Drakvik et al 2020

Addressing data and knowledge gaps

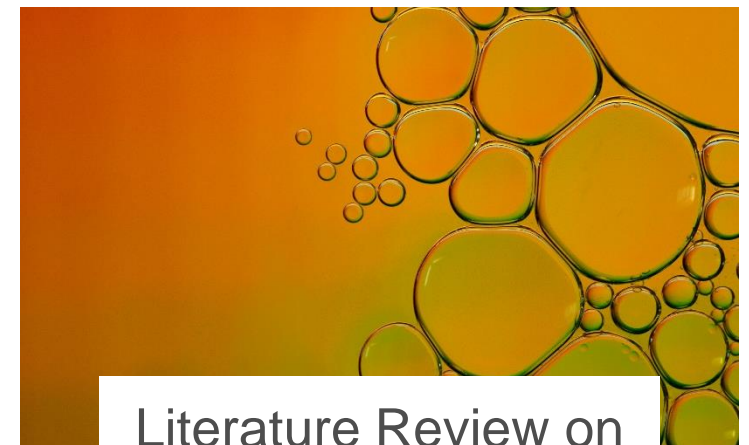


Sharing occurrence data

<https://ipchem.jrc.ec.europa.eu/>



Use of New Approach Methodologies for mixture risk assessment



Literature Review on Interactions



Addressing data and knowledge gaps

Exposure

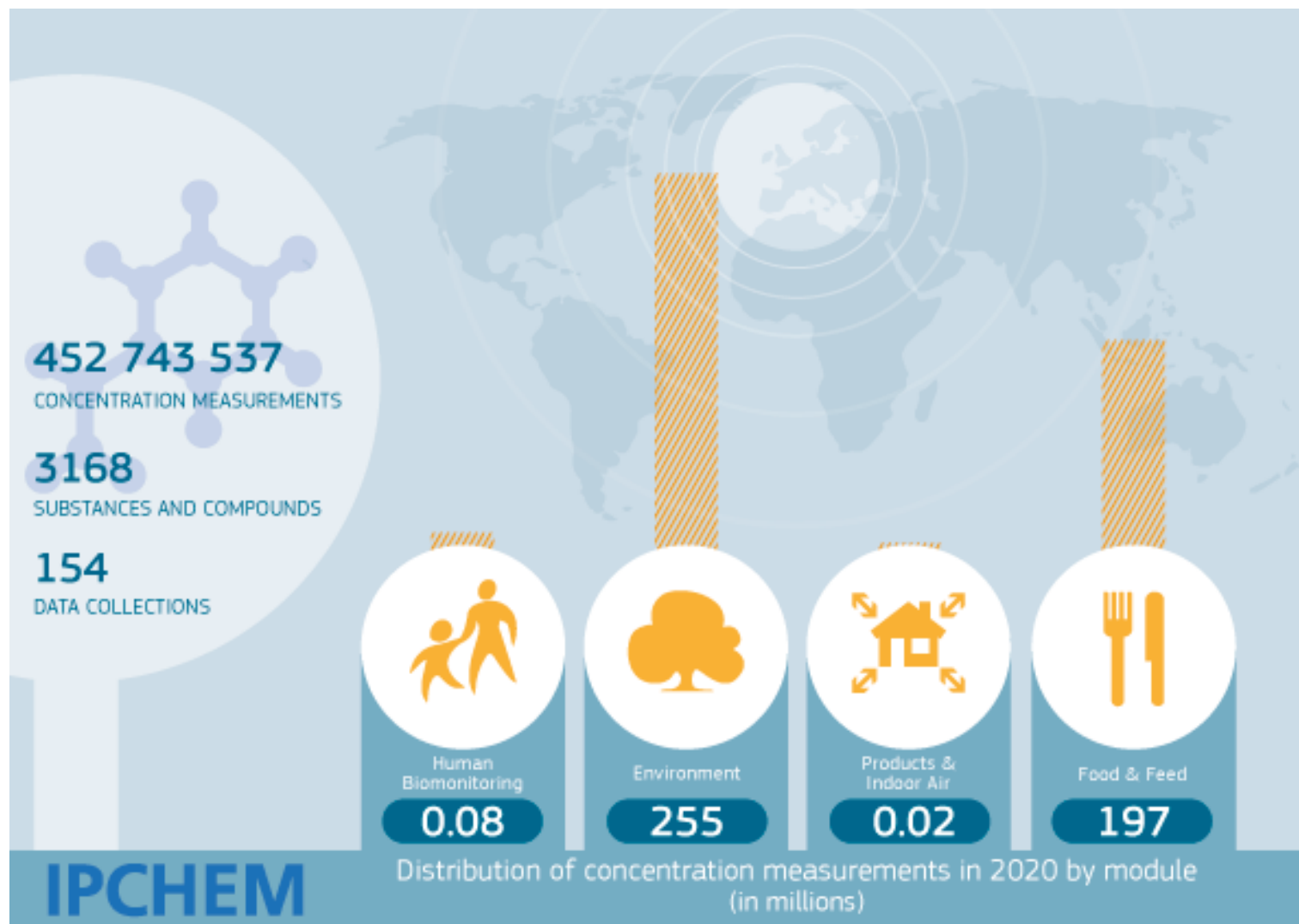
What is IPCHEM?

- Information Platform for Chemical Monitoring
- **Single access point for searching, accessing and retrieving chemical occurrence data** collected and managed in Europe and beyond

<https://ipchem.jrc.ec.europa.eu/>



What can you find in IPCHEM?



Harmonised & quality checked



Metadata & contact point



Share data publicly



How to use IPCHEM?

Information Platform for Chemical Monitoring
Enhancing access to chemical data

EUROPEAN COMMISSION > EU Science Hub > IPCHEM

Home Search Your basket Your viewer Share

Search Chemical:
Type chemical name/synonymous
Type chemical CAS number

Refine by module (optional)

Optional filters
Select media (optional)
Select project/institution (optional)
Select date (optional)

Advanced Search

General Human Biomonitoring Environment Food & Feed Indoor Air

Frequency Data granularity in IPCHEM Level of coverage

Country (optional):
Europe World Select Country List

Starting from a chemical or CAS number

EMODNETCHEM Data Access: Public
EMODnet Chemistry marine dataset of contaminants

Click HERE to start bounding

Sampling Matrix

You are searching:
Chemical Name : cadmium
CAS Number : 7440-43-9
Media : none
Country Name : undefined

Filter by Concentration:
Unit of Measure :

Exclude Non-Detects:
LOD LOQ none

Exclude QA Issues:
yes no

Show sample sites by page Show all sample sites Show sample sites by location

Home Search Your basket Your viewer Login

Your Basket

Search: [] Show 10 entries

		Chemical name	CAS	Country	Database	Criteria	Status	Viewer
1	<input type="checkbox"/>	cadmium	7440-43-9	undefined	AIRBASE	●	ready (pick) [500]	🌐
2	<input type="checkbox"/>	cadmium	7440-43-9	undefined	EMODNETCHEM	●	ready (pick) [500]	🌐
3	<input checked="" type="checkbox"/>	cadmium	7440-43-9	undefined	ESBUBA	●	ready (pick) [500]	🌐

Showing 1 to 3 of 3 entries

Policy/scientific questions IPCHEM can help on

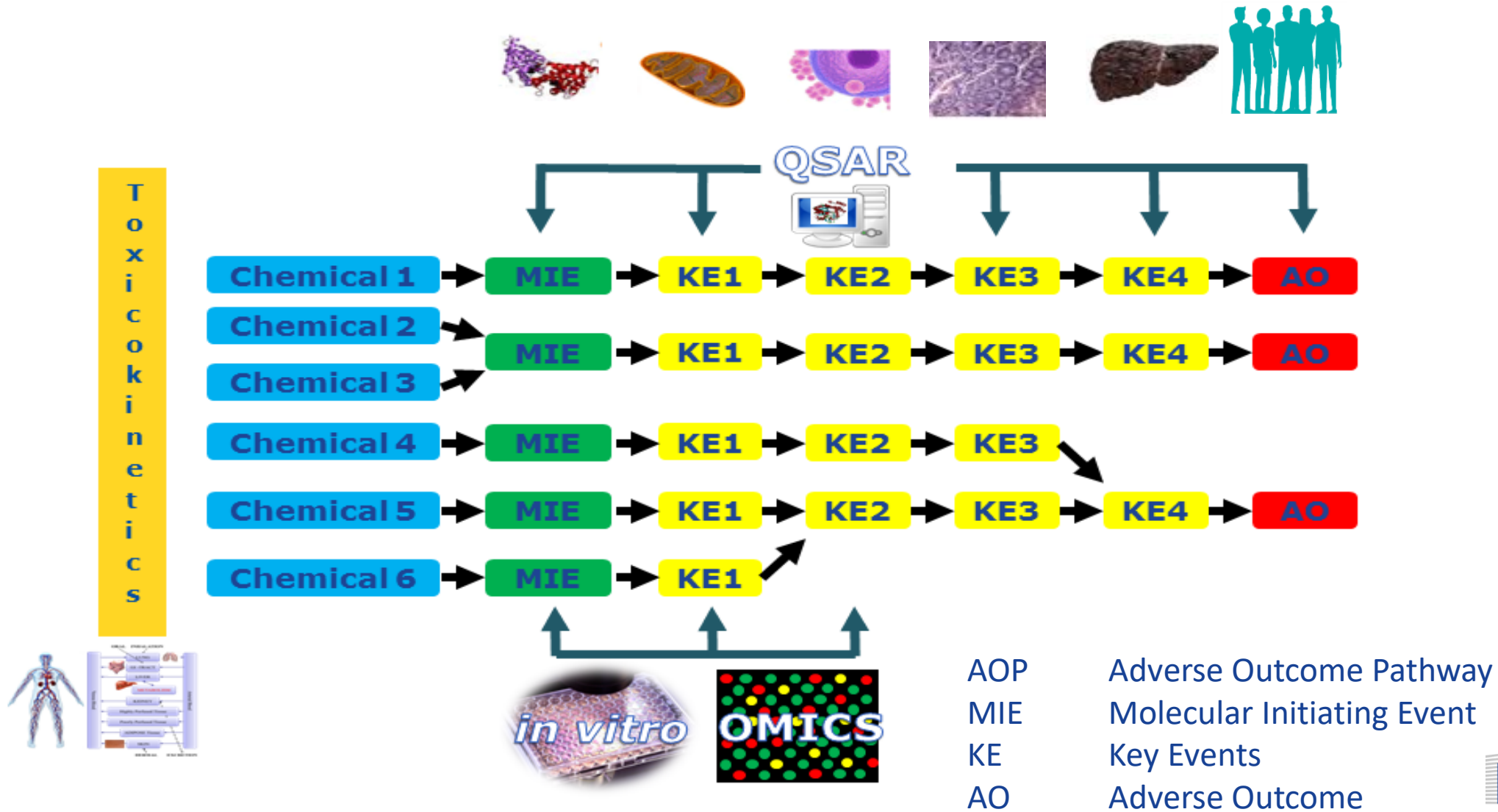
- Monitoring time and spatial trends 
- Risk/impact indicators 
- Monitoring compliance and targeting intervention 
- Impact of regulatory intervention 
- Regulatory risk assessments
- Explore aggregate and combined exposures



Addressing data and
knowledge gaps

*New approach
methodologies (NAM)*

Use of New Approach Methodologies (NAM)



Bopp et al (2019) *Critical Reviews in Toxicology*, 49(2), 174-189.
doi:10.1080/10408444.2019.1579169

Developmental neurotoxicity (DNT) mixture study

Aims

- Building on a **battery of *in vitro* assays** anchored to **common key events** (CKEs) identified in the DNT AOP network using human neuronal/glial culture to identify chemicals associated with **impairment of learning and memory in children**
- Determine whether chemicals combined at **individual non-neurotoxic concentrations** will produce **DNT effects in mixtures**

Chemical selection

1. Compounds known to cause cognitive impairment (AO)
2. Compounds acting through identified common KEs in the AOPs
3. Compounds representing different classes (i.e., pesticides, industrial chemicals, heavy metals, POPs, and EDs)
4. Compounds found in human samples (e.g., breast milk, cord blood, urine, hair, umbilical cord plasma, brain tissues, maternal blood, or blood of children)
5. Compounds according to EFSA (2013) working through:
 - similar MoA
 - dissimilar MoA



Exposure patterns of UV filters, fragrances, parabens, phthalates, organochlor pesticides, PBDEs, and PCBs in human milk: Correlation of UV filters with use of cosmetics

Margret Schlumpf^{a,*}, Karin Kypke^b, Matthias Wittassek^c, Juergen Angerer^{c,1}, Hermann Mascher^d, Daniel Mascher^d, Cora Vökt^e, Monika Birchler^e, Walter Lichtensteiger^a



European Food Safety Authority

EFSA Journal 2013;11(12):3472

SCIENTIFIC OPINION

Scientific Opinion on the relevance of dissimilar mode of action and its appropriate application for cumulative risk assessment of pesticides residues in food¹

EFSA Panel on Plant Protection Products and their Residues (PPR)^{2,3}



GUIDANCE

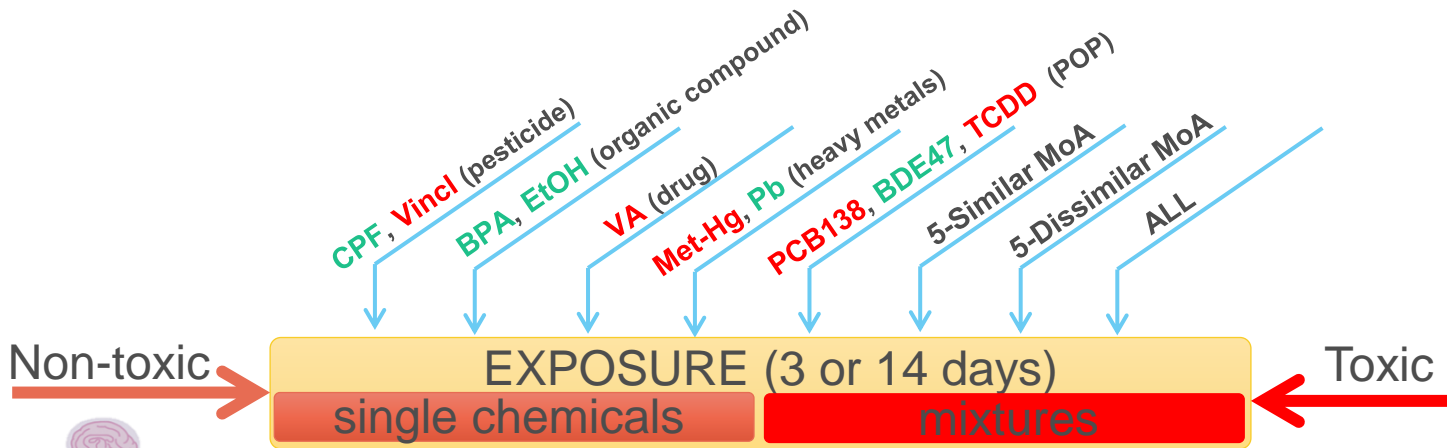
ADOPTED: 20 February 2019

doi: 10.2903/j.efsa.2019.5634

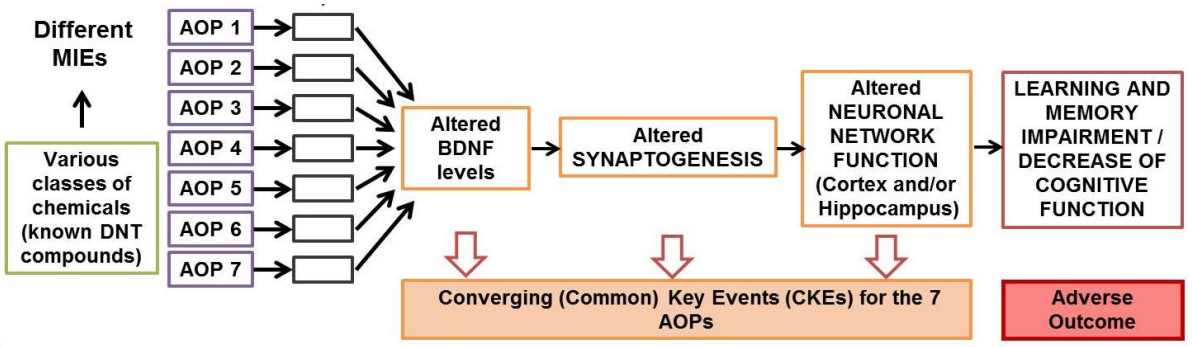
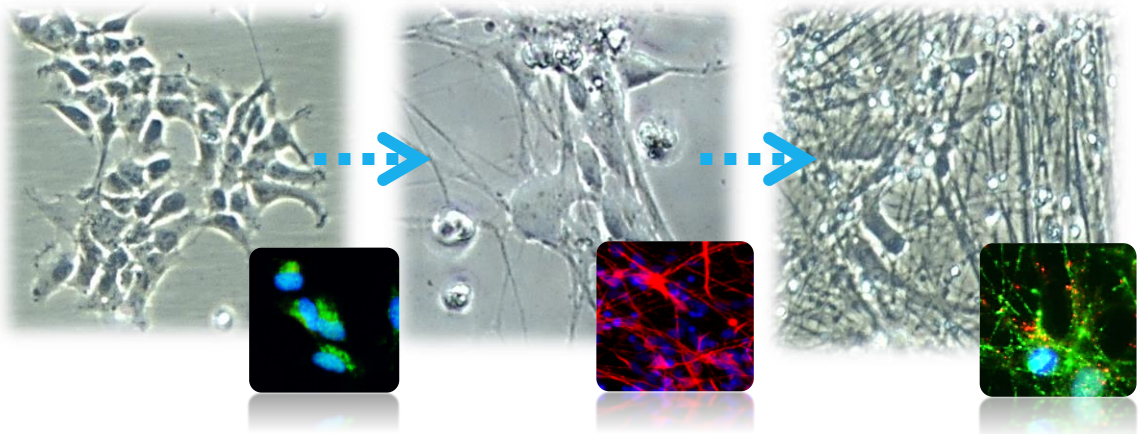
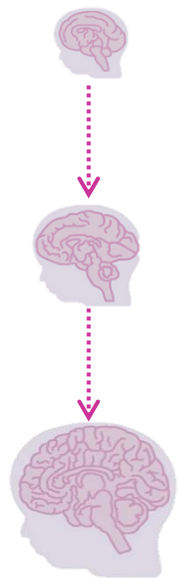
Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals

EFSA Scientific Committee,
Simon John More, Vasileios Ravnidis, Diane Benford, Susanna Hougaard, Bennekou

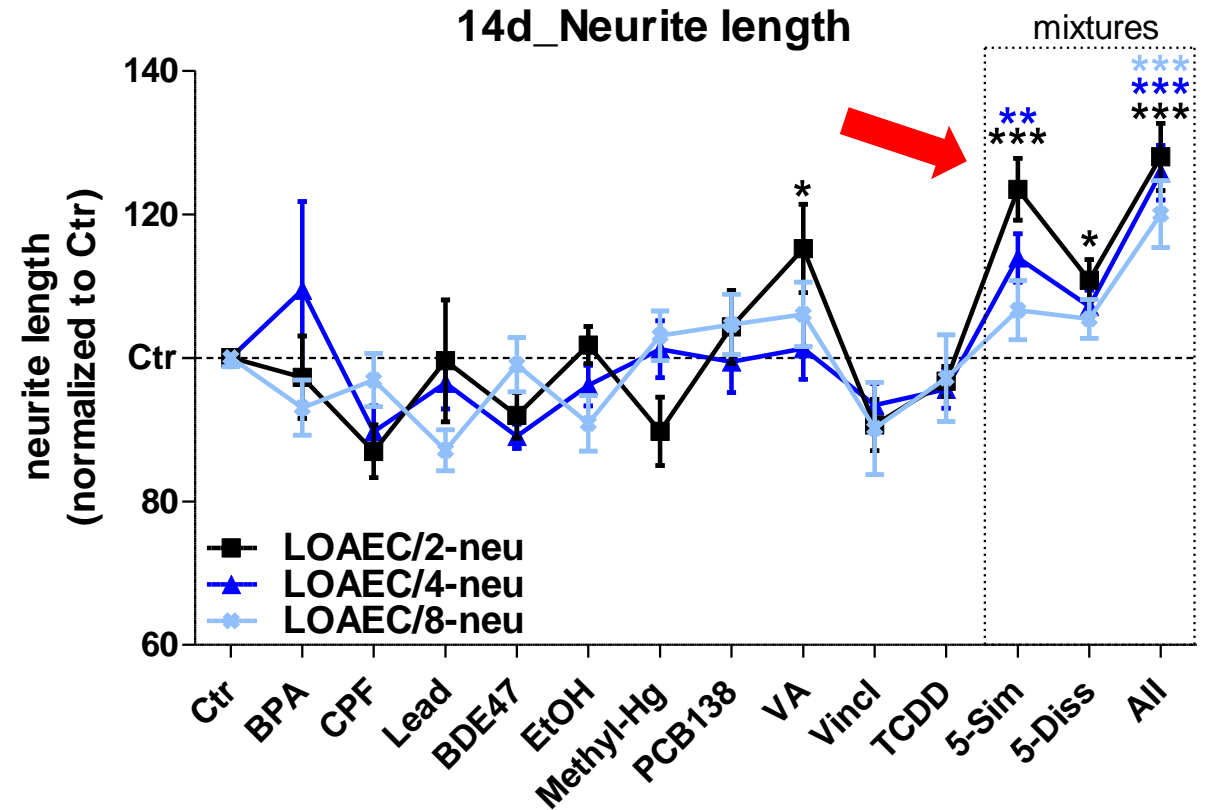
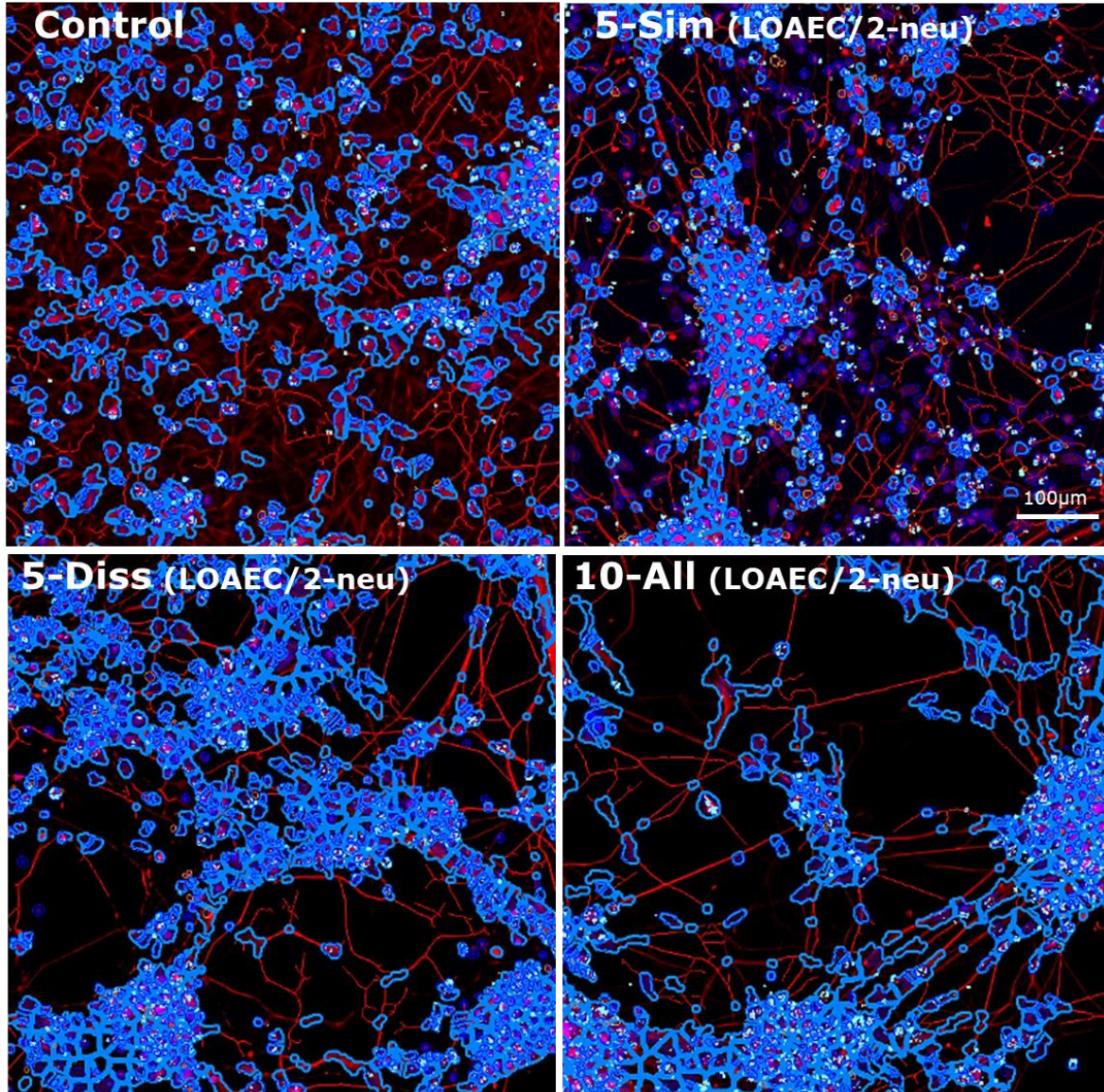
similar MoA - decreased BDNF level
dissimilar MoAs



Human in vitro neuronal model derived from iPSCs



Mixtures' effects on neurite outgrowth

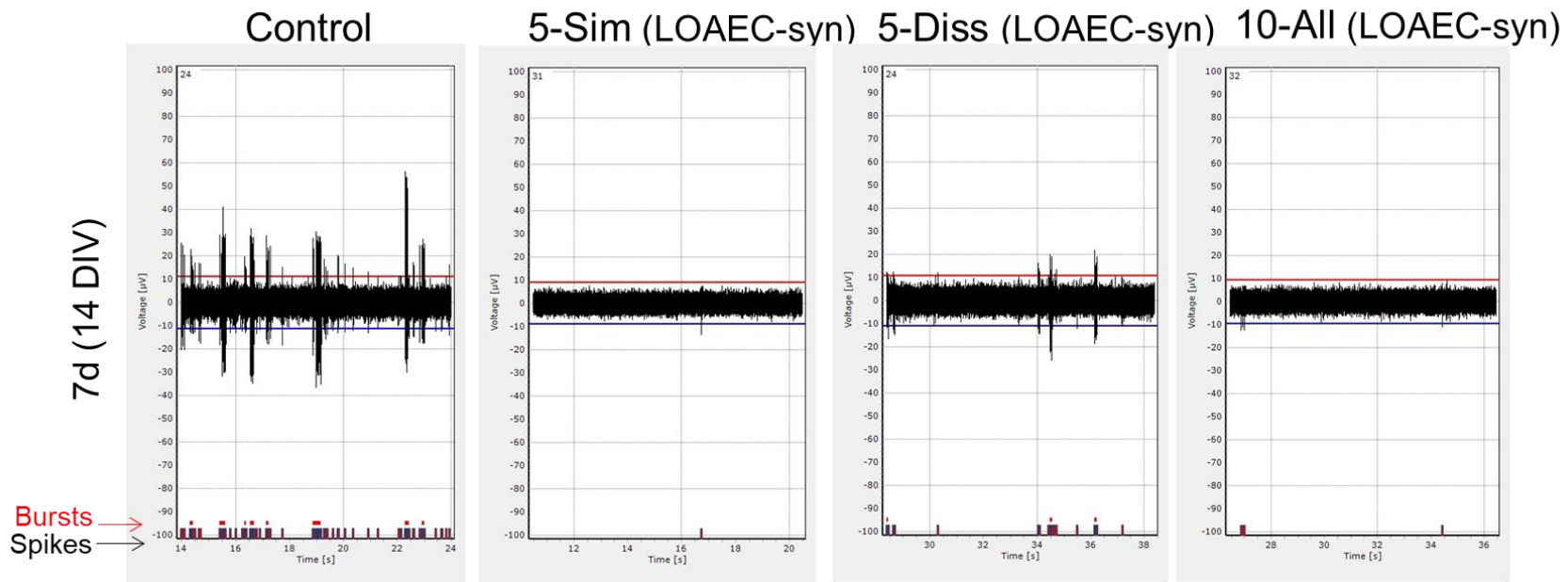
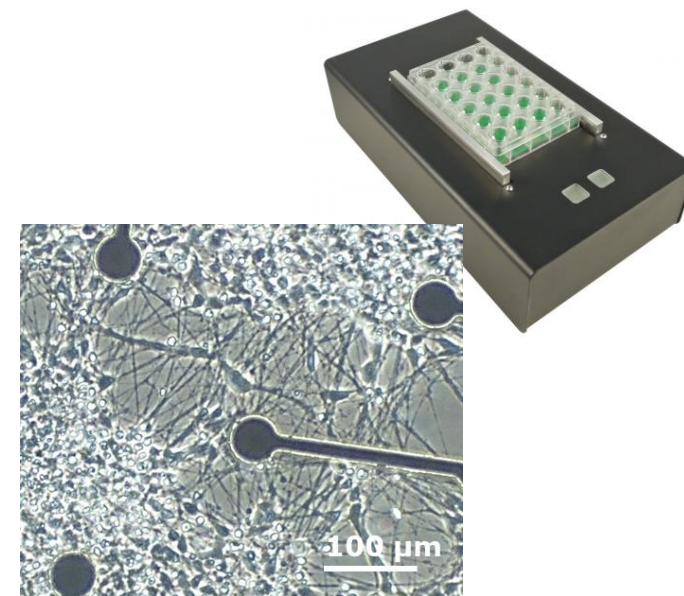
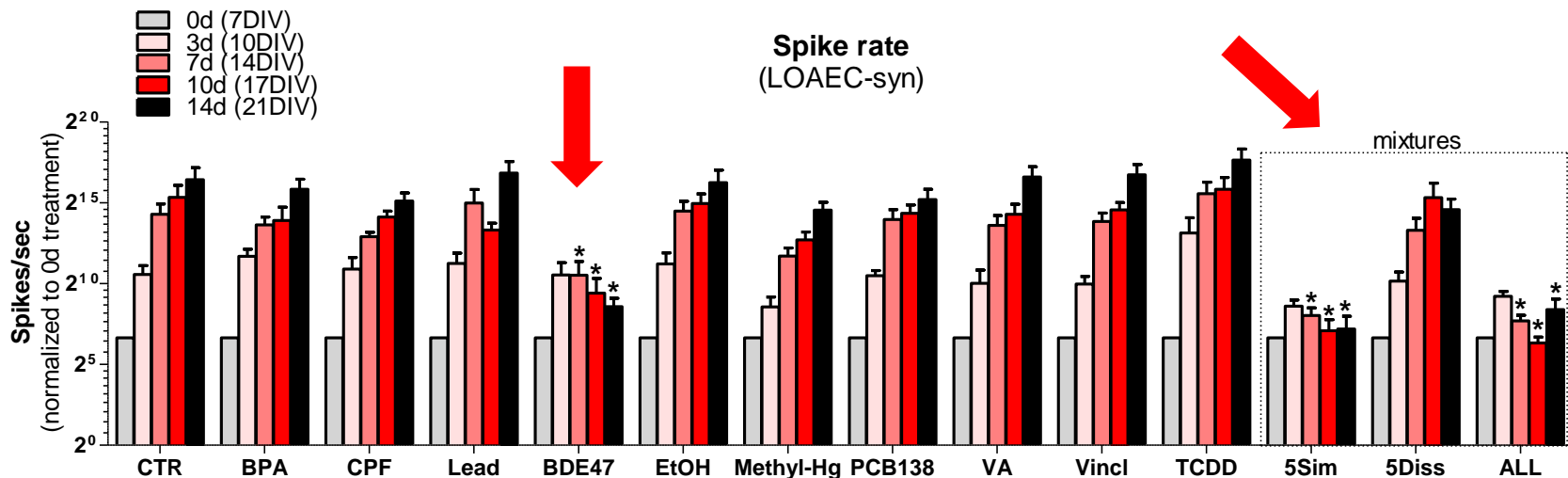


→ Increase of neurite length by 5-Sim and 10-All mixtures

Masks: valid nuclei / selected cell bodies / neurites / branch points

β -III-Tub DAPI

Mixtures' effects on electrical activity



→ **Decrease of electrical activity by 5-Sim and 10-All**

→ **BDE47 main driver of mixtures' effects**

Conclusions DNT experimental study

- **Common Key Events** identified in DNT AOPs guided selection of the in vitro assays, permitting **mechanistic understanding** of toxicity
- Low concentrations (i.e., below LOAECs) of single chemicals (non-neurotoxic) become **neurotoxic in mixtures**, especially for the chemicals working through **similar MoA**
- Human iPSC-neurons/astrocytes exposed to chemical mixtures at low concentrations **reproduce some features described in neurodevelopmental deficits** (e.g., increased BDNF, higher % of neurons and astrocytes, decreased synapses, etc.)



Addressing data and knowledge gaps

Interactions

Do we need to worry about interactions?

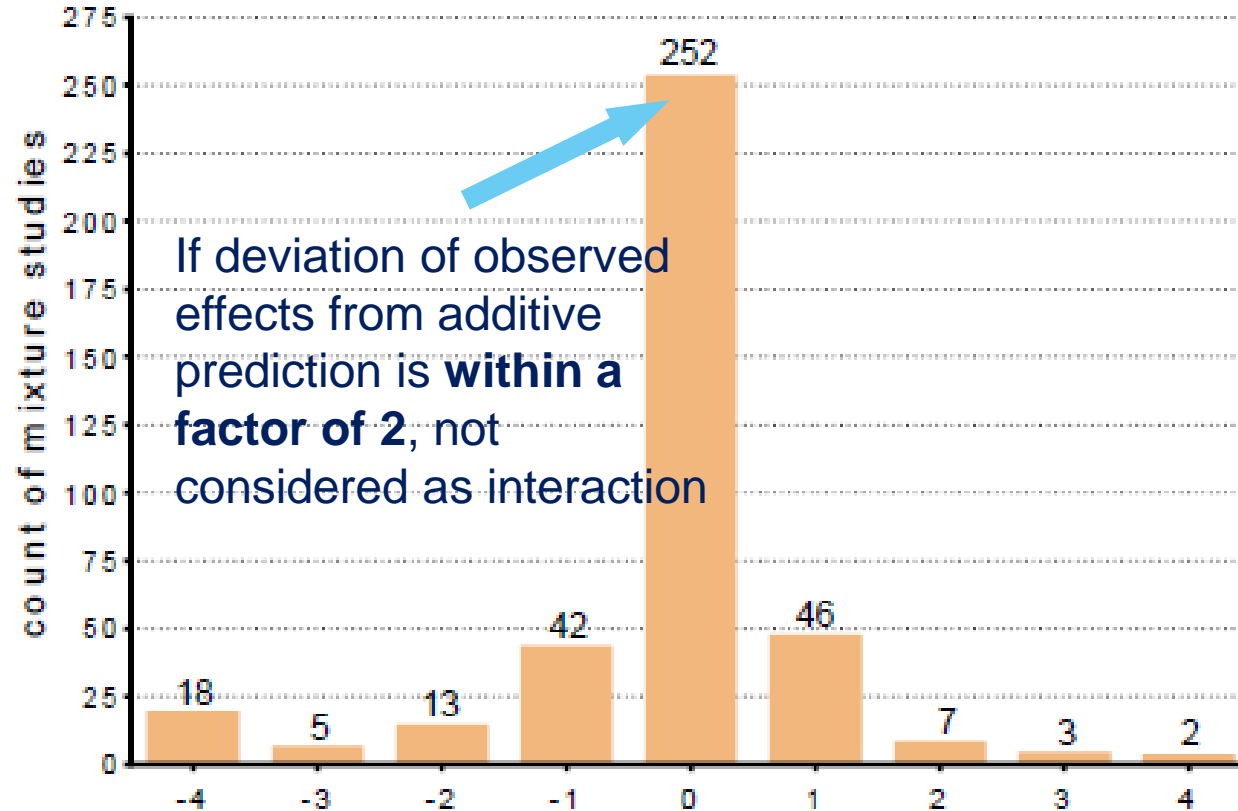
10790 papers

1205 papers
after abstract
screening

761 papers
after full text screening

1220 experiments
included

389 experiments
re-appraised

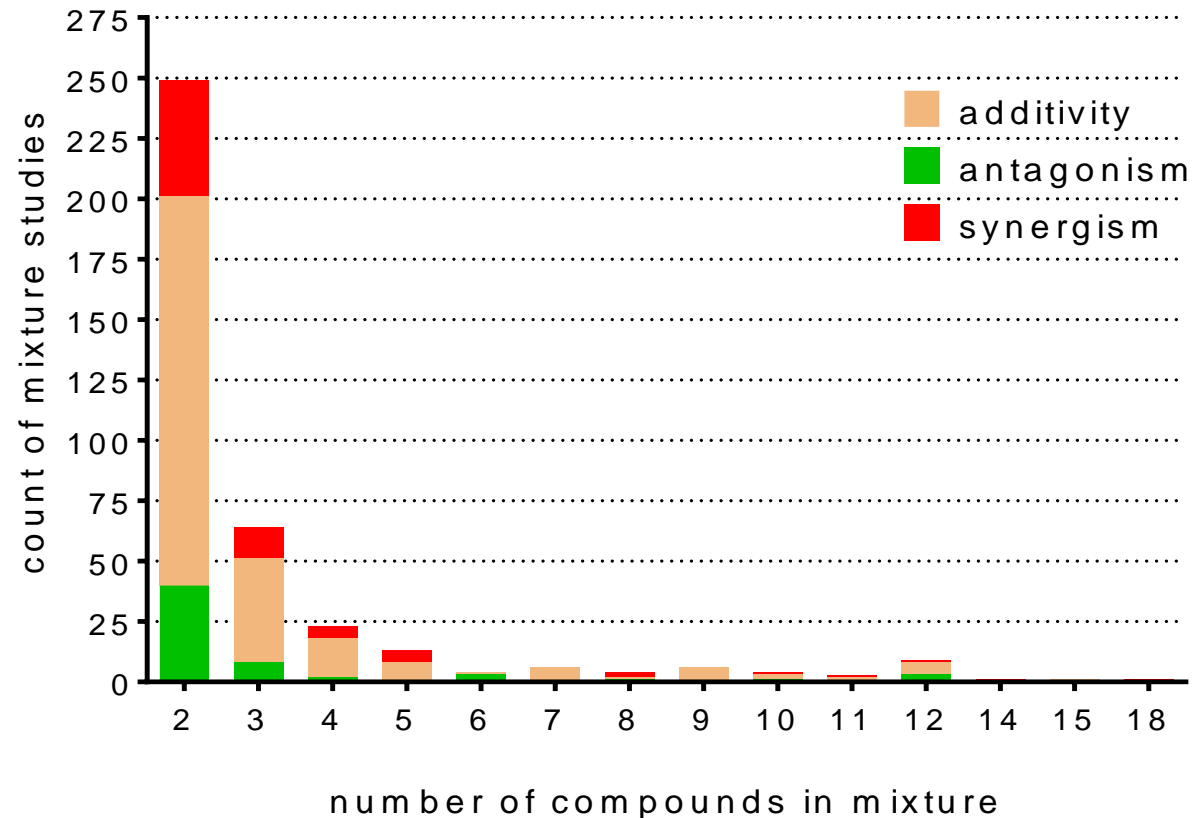


Class	-4	-3	-2	-1	0	1	2	3	4
IPQ range	<-700%	-700%	-500%	-300%	-100%	100%	300%	500%	>700%
	700%	500%	300%	100%	100%	300%	500%	700%	

← synergisms | antagonisms →

IPQ=Index of Prediction Quality
 Example:
 IPQ = 50% means that the observed effect concentration of the mixture is 50% above the predicted value,
 IPQ = -50% refers to an observed effect concentration of the mixture that is 50% below the predicted value

Do we need to worry about interactions?



Martin et al (2021) Ten years of research on synergisms and antagonisms in chemical mixtures: A systematic review and quantitative reappraisal of mixture studies, *Env Int*, 146, 106206, <https://doi.org/10.1016/j.envint.2020.106206>

Conclusions on Interactions (1)

- **65% of studies considered additive**
- synergisms as likely as antagonisms
- non-additivity slightly more frequent in *in vitro* studies
- deviations from additivity **mostly small**
- **large deviations** from additivity are more likely to occur as synergisms
- **strong synergisms** rare (effects at doses 50 to 100-times lower than expected based on dose addition)
- 47% of synergistic or antagonistic of higher **risk of bias** (compared to overall 38.5% for mixtures classified as additive, statistically not significant)
- **chemical groups** in the synergistic cases: number of cases with EDs (mechanistic basis is unclear) and cases for metals (CrVI, Ni with Cd), confirmation for chemicals such as triazines, azoles and pyrethroids

Conclusions on Interactions (2)

- No new evidence of synergisms at low doses, close to points of departure of the individual components
- Results confirm the utility of default application of the dose (concentration) addition concept for predictive assessments of simultaneous exposures to multiple chemicals
- Application of dose addition must however be complemented by an awareness of the synergistic potential of specific classes of chemicals
- (consider the classes of chemicals included in the underlying studies)

Thank you

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Nikolaos Parissis
Jutta Triebe
Elisabet Berggren

Brunel University team for work on
interactions



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