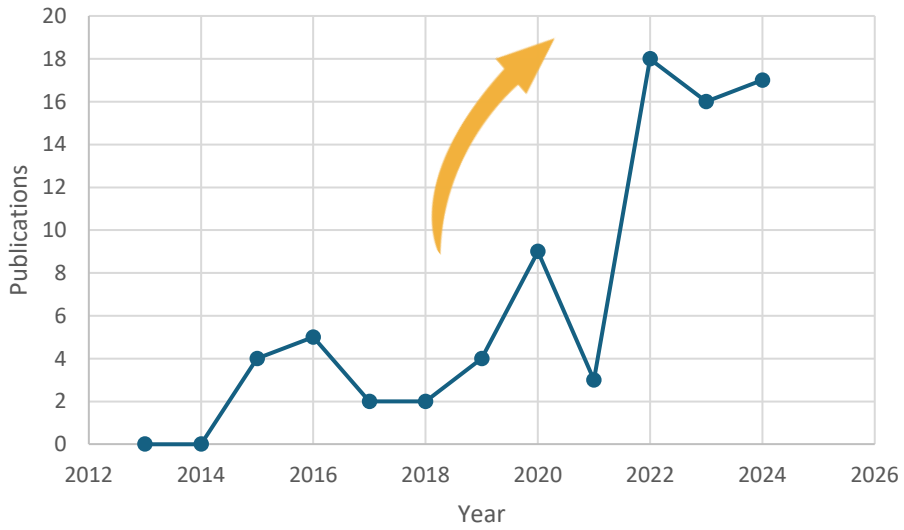
Current NAMs applied to chemical toxicology evaluation

Data types and **regulatory relevance**

Silvia Dominguez, Jérémie Théolier, & Samuel Godefroy

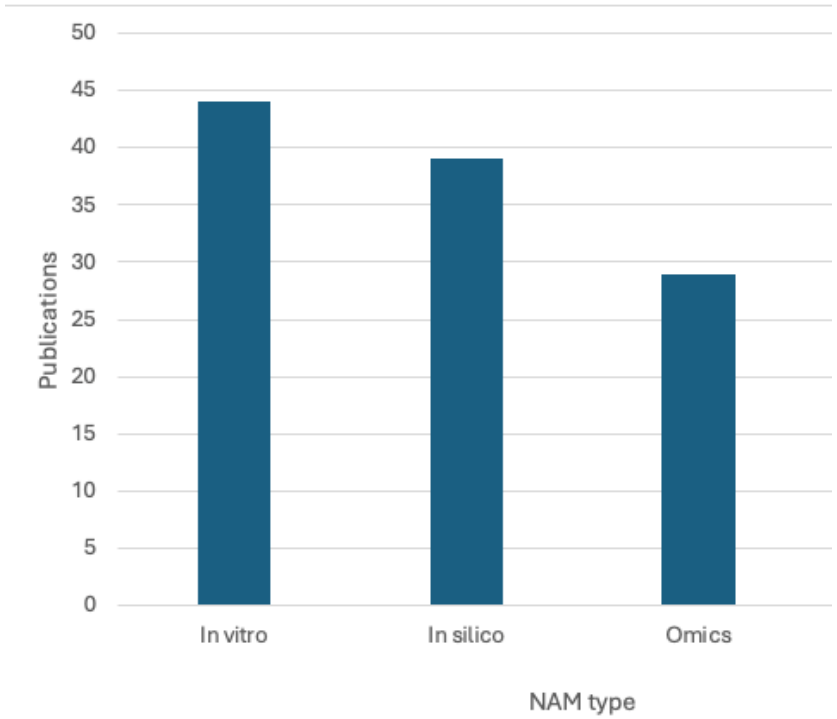
Scoping review

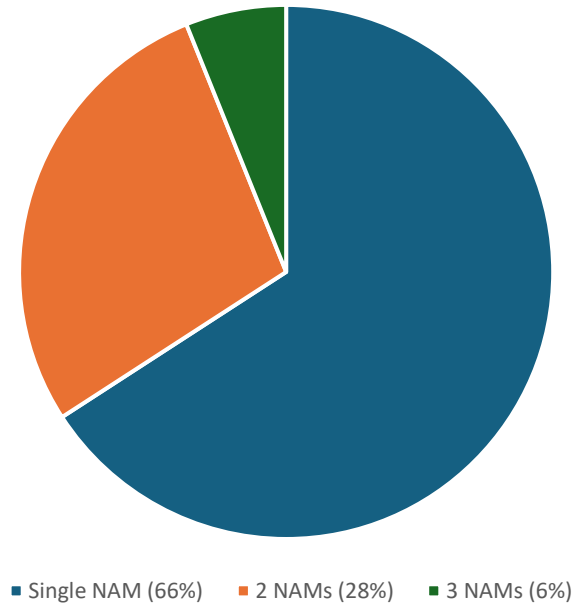


Classification	Number of publications	Affiliations included
JECFA	25	JECFA
OECD	15	Health Canada; BIAC; EU/JRC; ICAPO; EU ToxRisk; OECD “project team”; Academic or regulator related to OECD
Academic	12	Academic only (not agency-related)
US EPA	11	US EPA; Academic related to US EPA
EU-level agencies/initiatives	10	EFSA (scientific opinions/reports, but not safety evaluations); EC; EU ToxRisk; Academic related to EU agencies/initiatives
European national agencies	5	UK FSA; German Federal Institute for Risk Assessment; National Institute for Public Health and the Environment - The Netherlands; The Norwegian Institute of Public Health; Academic related to European national agencies
China National Center for Food Safety Risk Assessment (CFSA)	4	CFSA; Academic related to CFSA
Total	**82**	

Types and number of NAMs used

- If used in combination with traditional methods, only NAMs-related data was extracted





Test system / approach

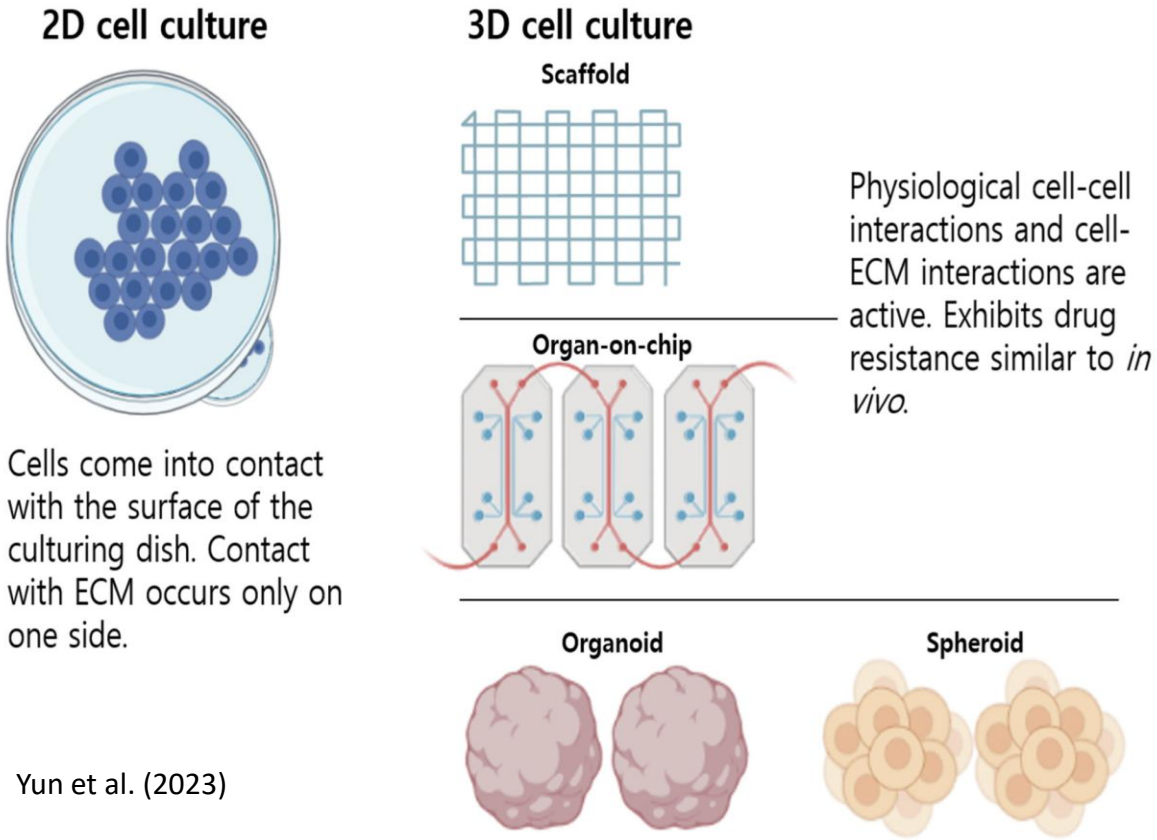
- Complex
- Broad categories

NAM type	Test system/approach	Number of publications
In vitro (n = 44)	Human cells / tissue models	19
	Battery assays / High throughput screening	13
	Mammalian cells / microsomes	7
	Other*	8
In silico (n = 39)	Structure-based (Grouping / Clustering / Read across / QSAR / Molecular docking)	19
	Metabolism-based (PBK models, QIVIVE, BMD models)	17
	Other predictive models (AO, toxicity, risk)	8
	Other*	6
	Toxicity database	5
Omics (n = 29)	Proteomics	21
	Transcriptomics	6
	Other*	2

Test system / approach

In vitro

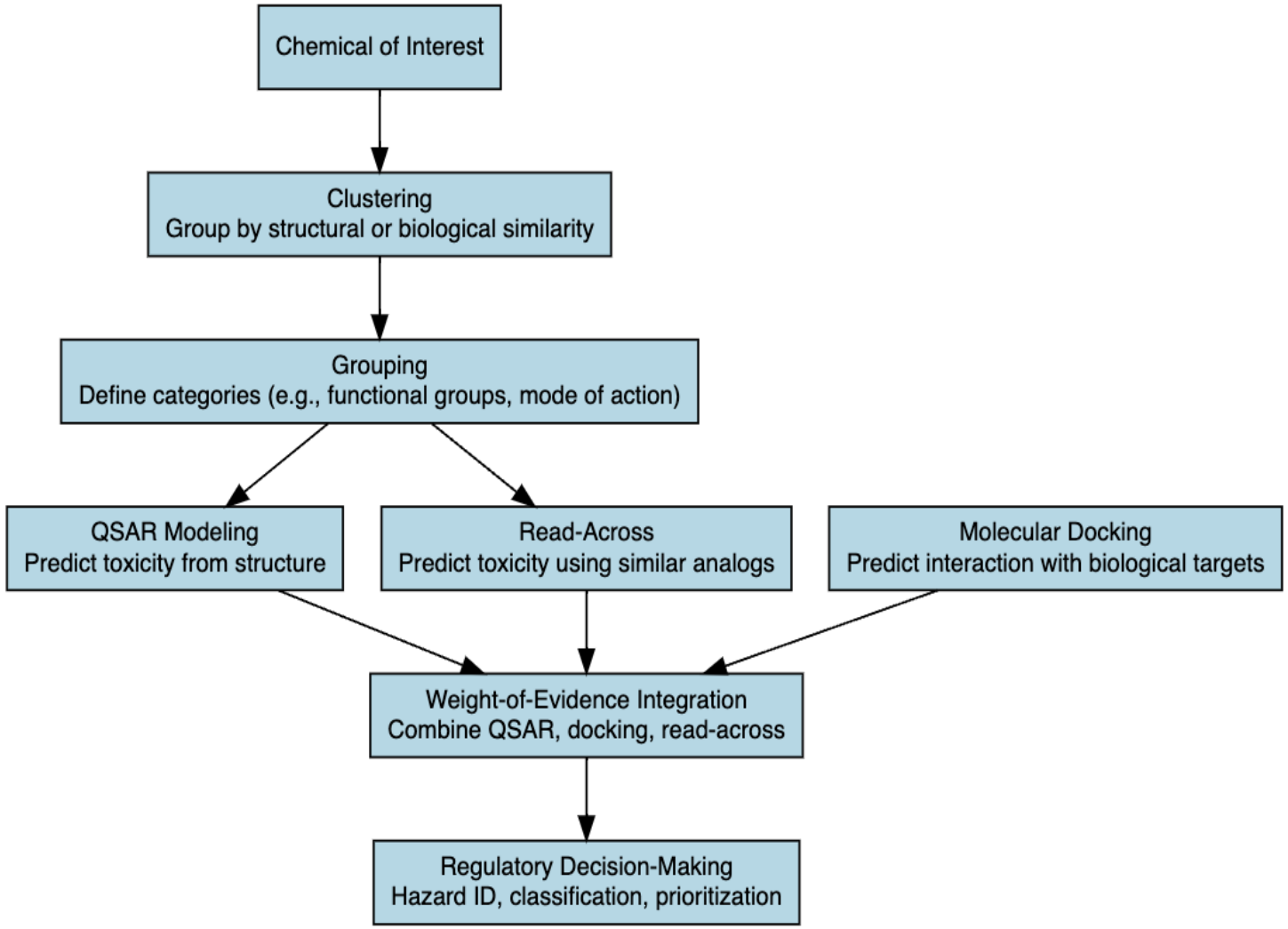
- Broad range of outputs / applications
- Systems with increasing levels of complexity
  - Mimic responses in humans
- Sets of assays
  - High throughput, battery
  - Purpose, scale, method



Yun et al. (2023)

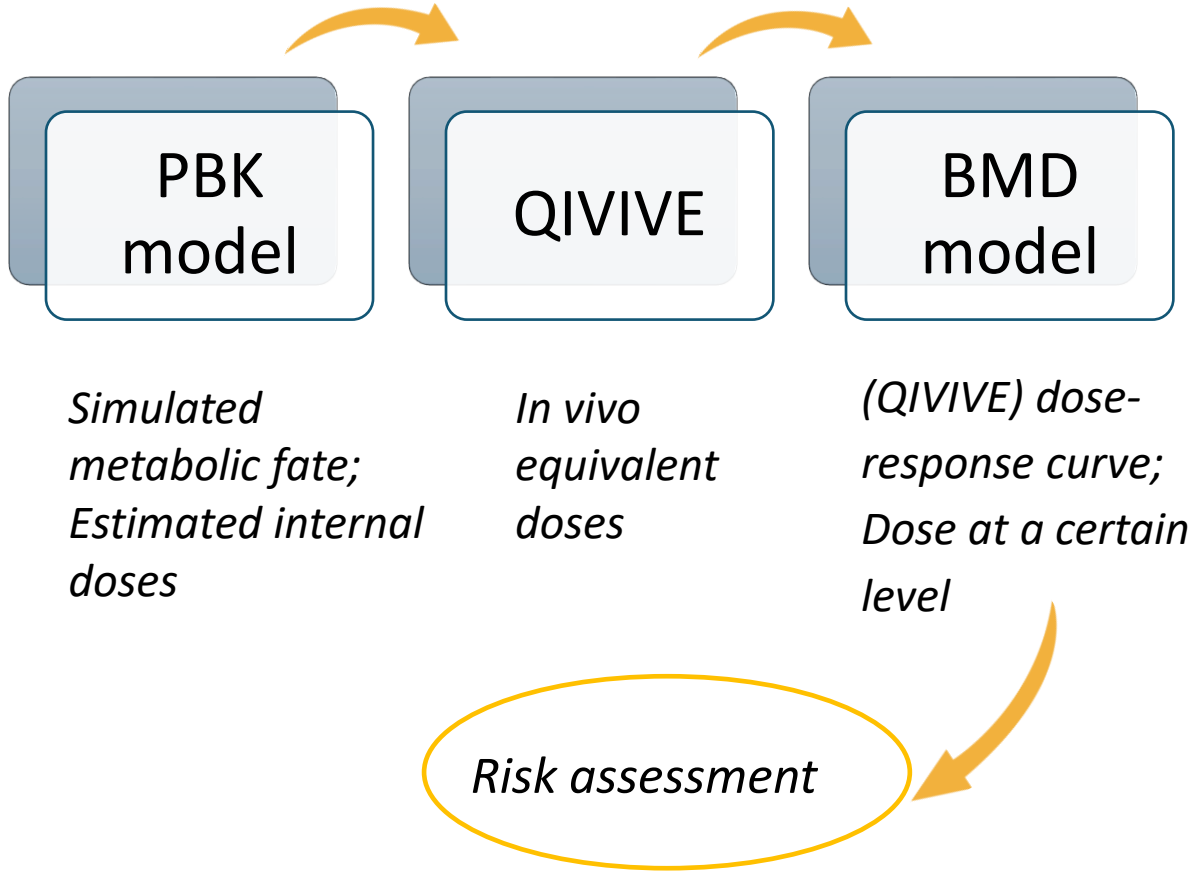
Test system / approach: in silico

- Structure-based
- Predicted toxicity of data-poor chemicals
- Hazard ID, prioritization



Test system / approach: in silico

- Metabolism-based
- Require toxicokinetics input data
- Dose = hazard characterization



Adverse Outcome Pathways (AOPs)

- Classic toxicology: **IS** this chemical toxic?
- With AOPs: **HOW** does it lead to toxicity?
- Link a molecular-level event to an adverse effect = predict toxicity
- Used in 1/3 of the reviewed documents, mostly for pesticides

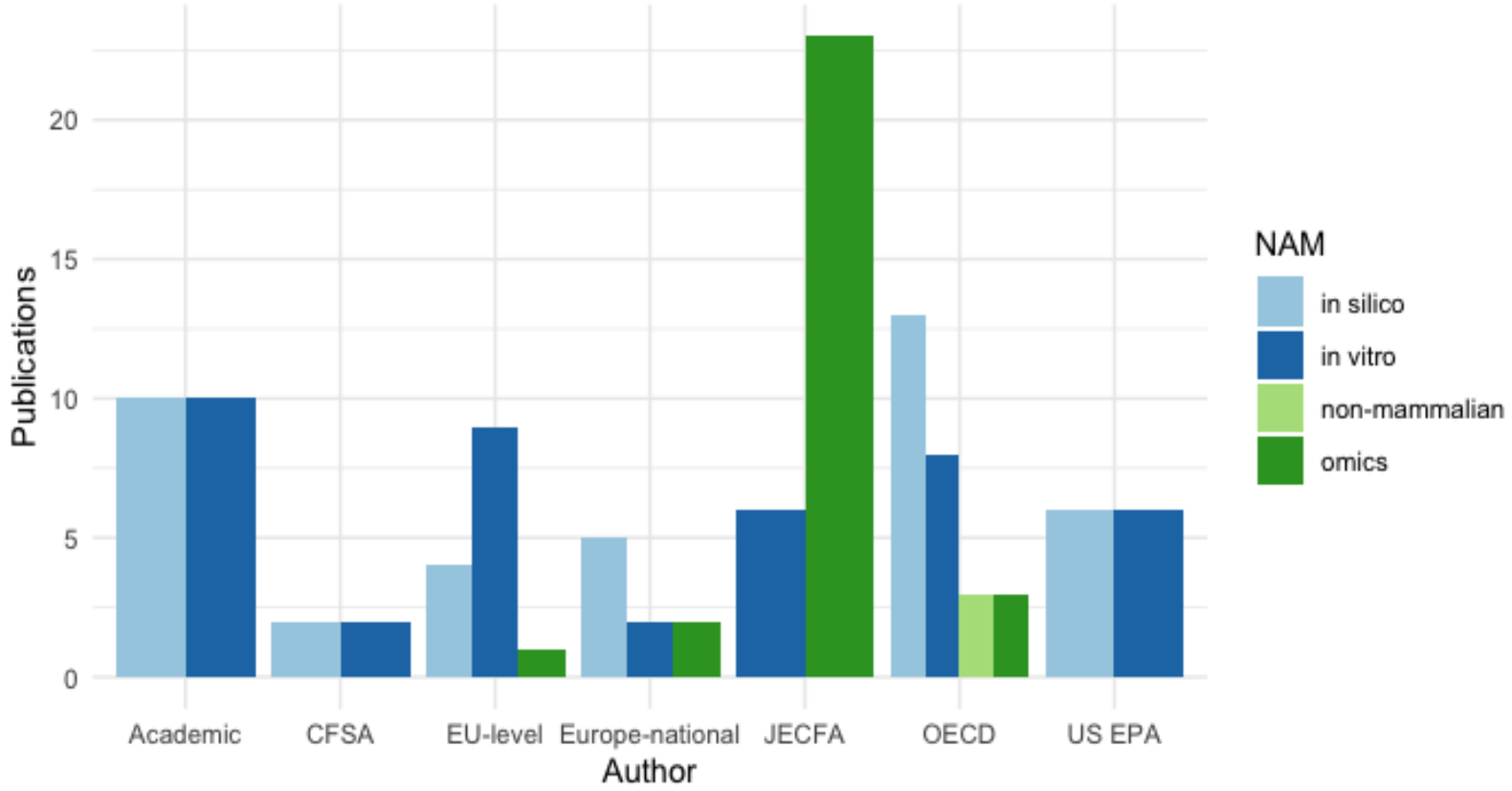
Hazard ID: biological plausibility

Hazard characterization: from key events' doses to exposure levels

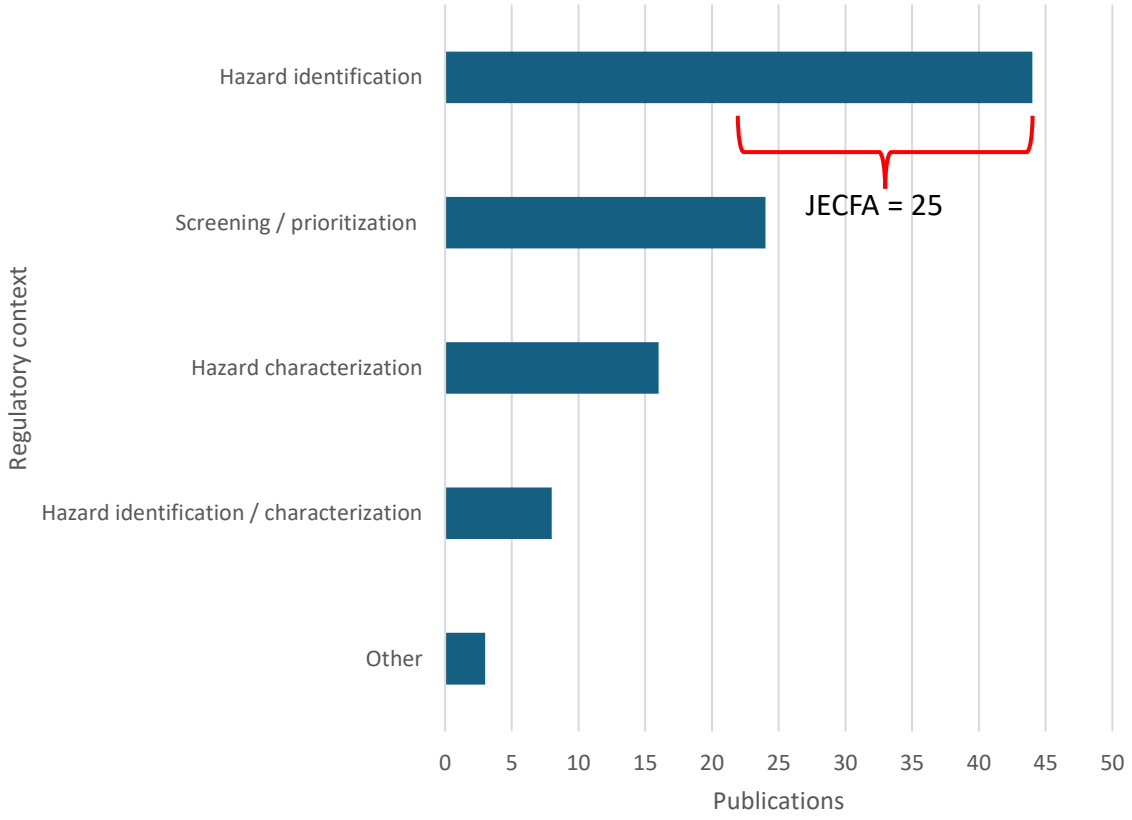
NAMs (in vitro, omics) that correspond to molecular events in the AOP

In silico NAMs (PBK, molecular docking)

NAMs use per author class

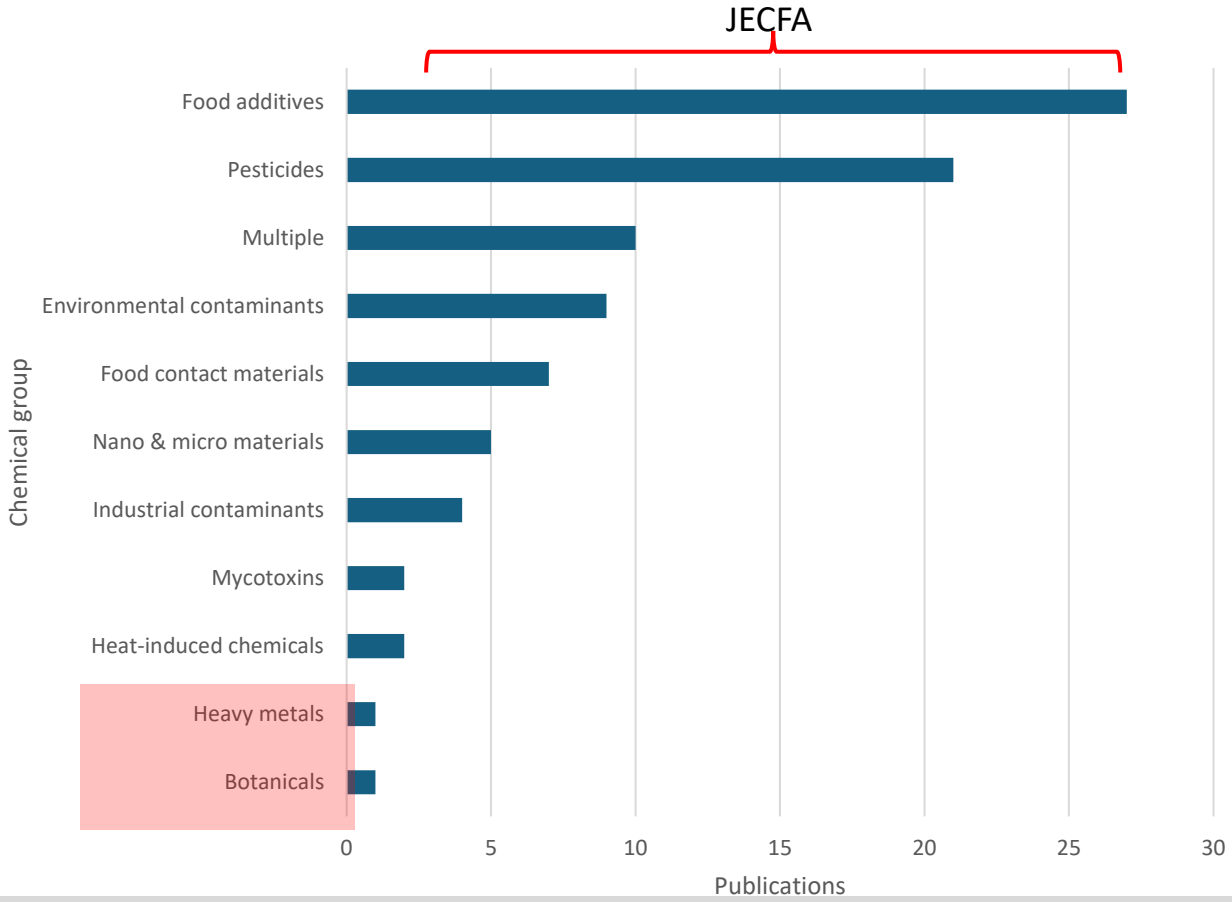


NAMs use per regulatory purpose



- Hazard ID (toxicity): effect of JECFA
- Screening/prioritization for further assessment: US EPA
- Hazard characterization (doses): OECD

Chemicals studied with NAMs



- Food additives: JECFA effect
- Pesticides: OECD
- Multiple: US EPA
- Academic sources: broadest variety of chemical groups

Toxicological endpoints studied with NAMs

Correlation with chemical targets

- Allergenicity, general toxicity: food additives
- Neurotoxicity: pesticides
- Genotoxicity, cytotoxicity: broad range of chemical groups
- Endocrine disruption: simultaneous assessment of multiple chemicals

Conclusions

- General portrait
- Broad coverage from different sources
- Acceptance of screening/prioritization applications
- Hazard characterization: in silico capabilities, need for mechanistic models and input data
- Difference between developments and adoption

Thank you