

Bridging the divide between scientific development and regulatory application

Maurice Whelan

European Commission, Joint Research Centre (JRC)

GSRS23, Parma (IT), Sept 2023

EU Reference Laboratory for
alternatives to animal testing
(EURL ECVAM)



Non-animal methods in science and regulation

EURL ECVAM status report 2022



Commission's response to the
European citizens' initiative

SAVE CRUELTY-FREE
COSMETICS – COMMIT
TO A EUROPE WITHOUT
ANIMAL TESTING

July 2023
#EUTakeTheInitiative

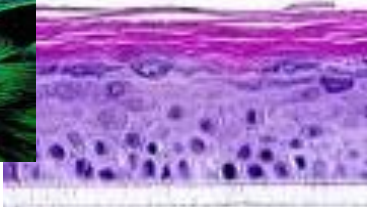
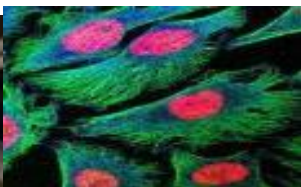
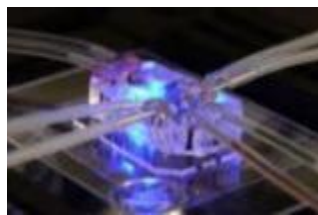


COMMISSION'S RESPONSE TO THE CITIZENS' INITIATIVE

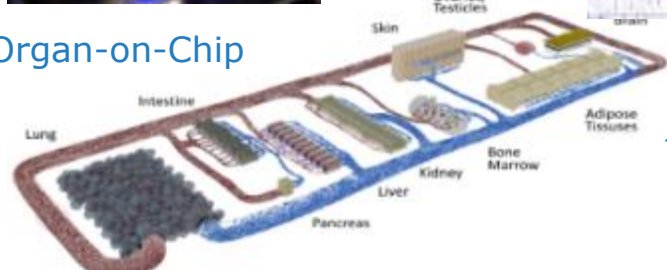
The Commission is proposing the following actions in response to the objectives of the citizens' initiative:

- ▶ continue to **apply and enforce the animal testing ban** in the framework of the EU Cosmetics Regulation;
- ▶ consider the need for legislative changes to further **clarify the interface between the EU Cosmetics and REACH Regulations** based on the outcome of an ongoing judicial review;
- ▶ kick off work on a roadmap **towards replacing animal testing in chemical safety assessments**, with multiple actions and a step-by-step path to replacing animal testing, involving all relevant stakeholders;
- ▶ initiate a series of actions to accelerate the reduction of **animal testing in research, education and training**, including exploratory workshops, and sustaining new training initiatives for early career scientists;
- ▶ continue to support research on alternatives to animal testing with **EU funding**.

Modern safety assessment toolbox

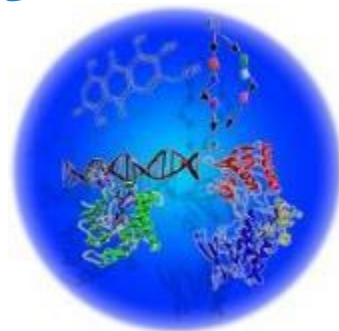


Organ-on-Chip



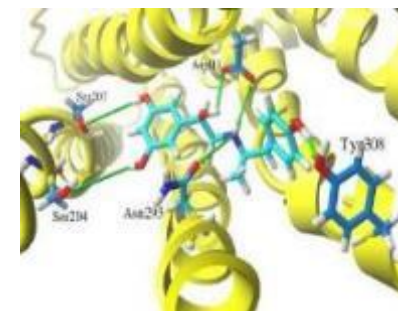
in vitro

QSAR

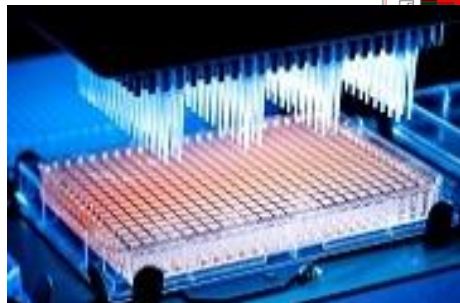
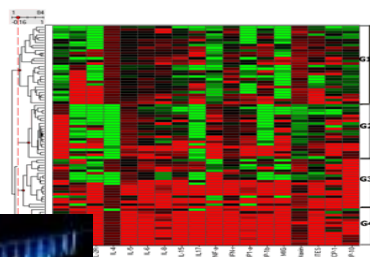


clinical data

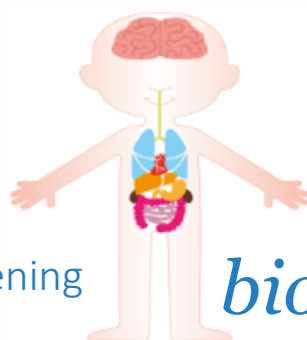
docking



'omics



High Throughput Screening



biokinetics



existing animal data



human biomonitoring

Why is uptake of **NAMs** relatively slow?



The Commission invested

> **€1 billion** into

> **300 projects**

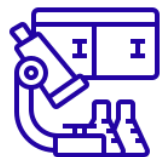
over the last two decades to develop alternative methods



limited awareness and confidence in **NAMs** from regulators



insufficient availability of **NAMs** to cover complex regulatory endpoints or all aspects of medical sciences



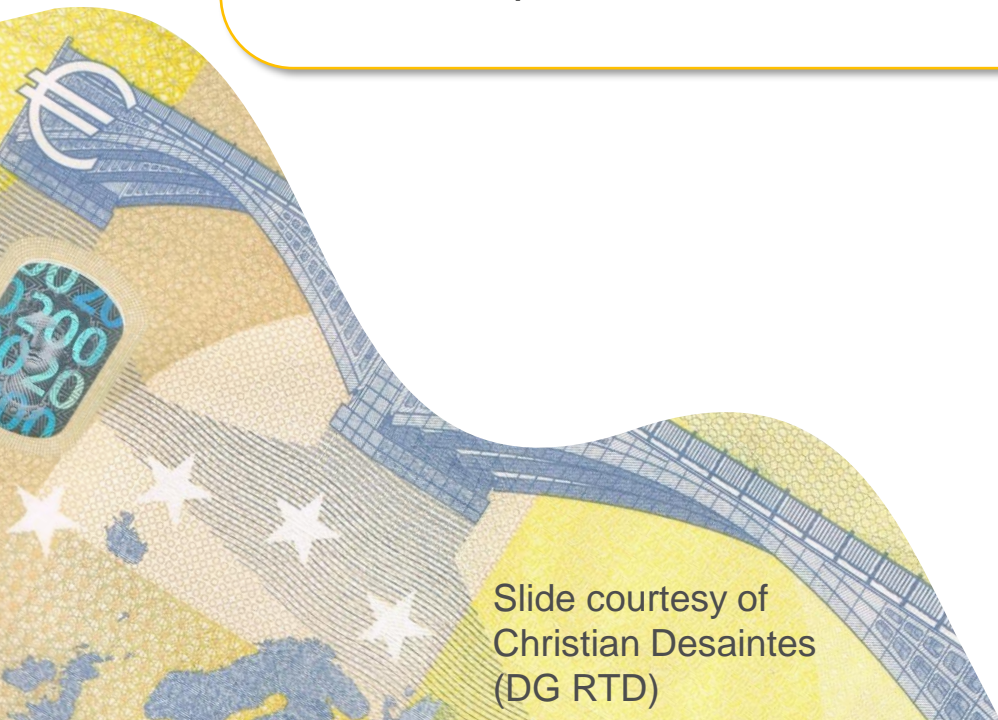
lack of investment in **MS** to fund additional **NAMs** and research facilities and equipment



lack of resources in **MS** to validate/qualify **NAMs**



limited coverage in **university teaching**

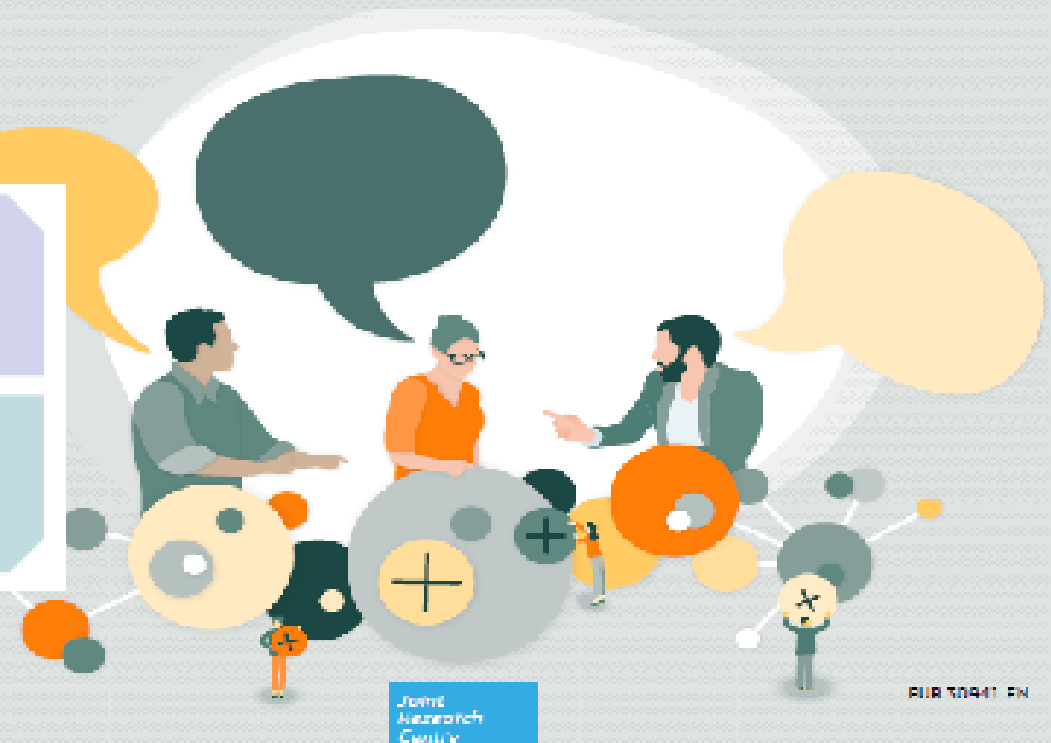


Slide courtesy of
Christian Desaintes
(DG RTD)

JRC survey on non-animal approaches

- Supporting action to extend REACH info requirements
 - Emphasis on regulatory applicability and deployability
 - Conducted online from June '21 to March '22
- **Many methods but little integration** - impressive technologies and tools but without clear application
 - **Demonstration rather than validation** - case studies popular for illustrating and discussing concepts
 - **A lot of variety but little standardisation** - many ways of generating different types of information

ADDRESSING EVIDENCE NEEDS IN CHEMICALS POLICY AND REGULATION



JRC Science for Policy Report (Feb 2022)

Current challenges in regulation of chemicals

- ▶ the science directly informing policy and regulatory decision-making often lags behind current science;
- ▶ there is a lack of consensus on different methods and approaches in toxicological sciences, exacerbated by difficulty of access to large quantities of dispersed and non-standard data;
- ▶ there is mistrust among stakeholders in different sectors;
- ▶ there is not a shared understanding of how data is constituted as evidence for regulatory decisions, or for current and future policy regarding chemicals;
- ▶ in view of the likely increasingly contentious nature of chemicals and other potential stressors, transparency of the decision-making process in regulation and policy, for all stakeholders, becomes an ever greater challenge.

JRC Science for Policy Report (Feb 2022)

So how do we **bridge** the divide?

What have a Swiss watchmaker, the Dalai Lama and Picasso got in common?!

Audemars Piquet: “To break the rules, you must **first master them**”



Dalai Lama XIV: “Learn the rules so you know how to **break them properly**”

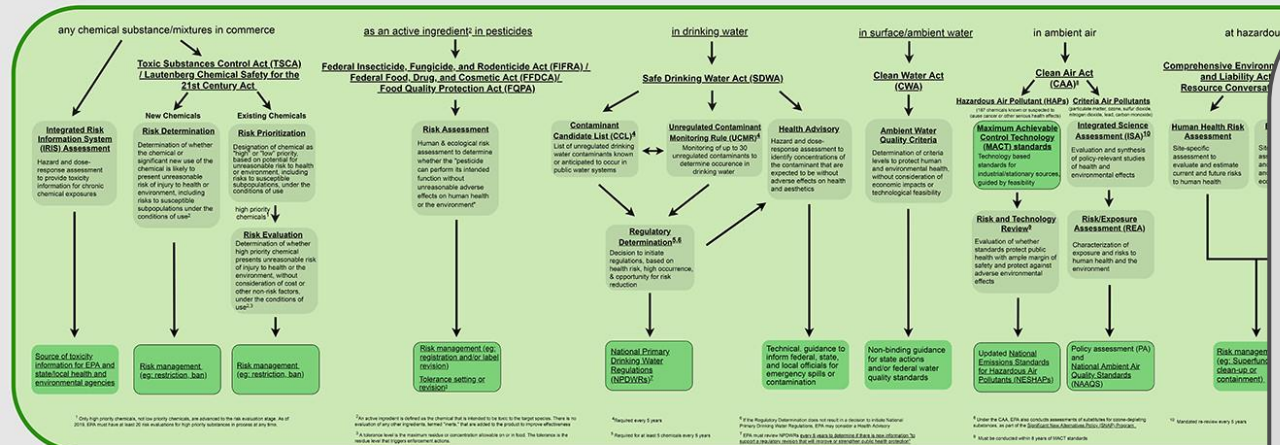
Pablo Picasso: “Learn the rules like a pro, so you can **break them like an artist**”

*Rules reflect context,
and context is everything*

Where is the chemical found or used?

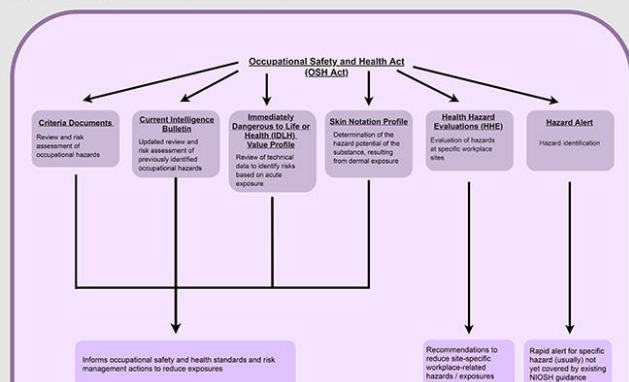
in the environment

EPA
Environmental Protection Agency



in the workplace

NIOSH
National Institute for Occupational Safety and Health

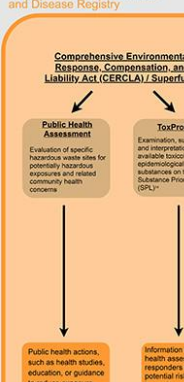


at hazardous waste sites

OSHA
Occupational Safety and Health Administration

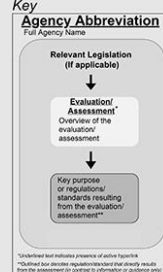
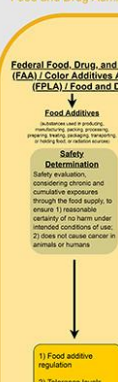


ATSDR
Agency for Toxic Substances and Disease Registry



in food or cosmetic

FDA
Food and Drug Administration



anywhere with public health concern

NIH/NIEHS/DNTP
National Institutes of Health/National Institute of Environmental Health Sciences/Durham National Toxicology Program

Agency

Relevant Legislation
(if applicable)

Evaluation/Assessment
Overview of the evaluation/assessment

Key purpose
or regulations/standards resulting from the evaluation/assessment

ENVIRONMENTAL
Science & Technology

“Environmental Health Risk Assessment in the Federal Government: A Visual Overview and a Renewed Call for Coordination”

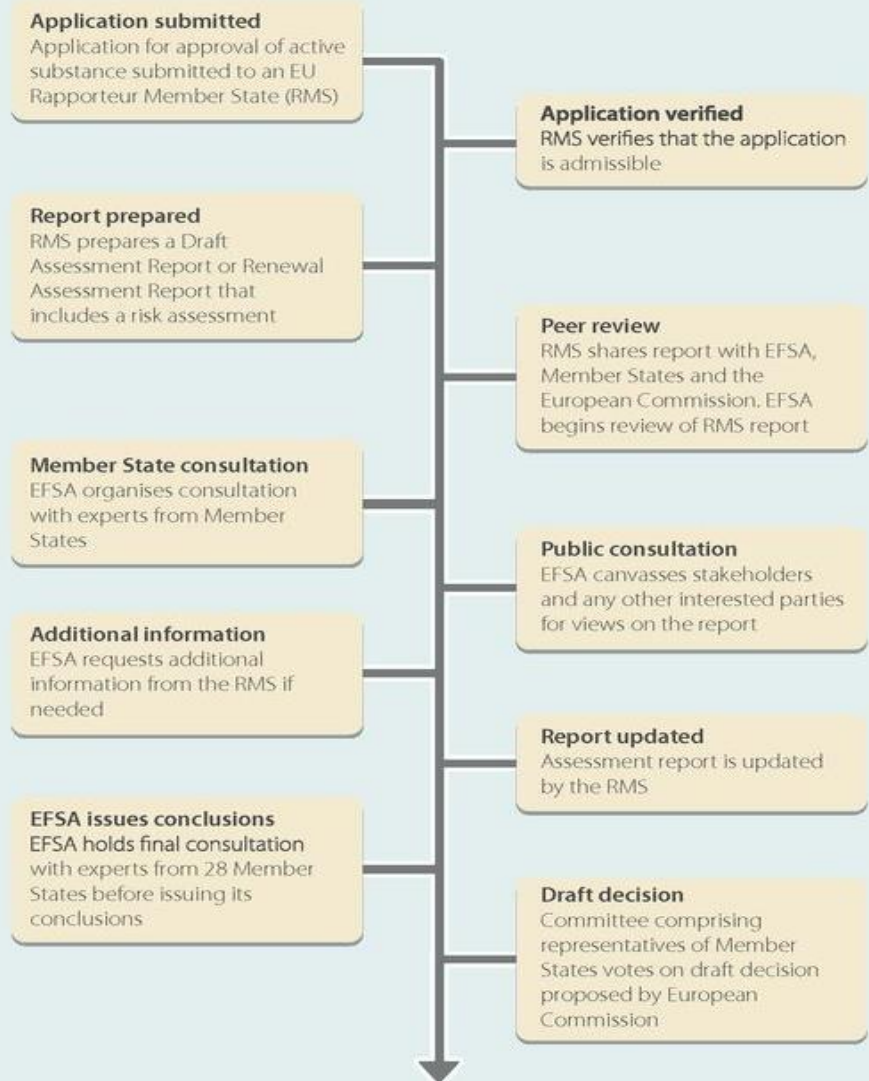
R. M. Shaffer (2021)
Environ. Sci. Technol., 55, 10923–10927



Landscape of the EU

WHO ASSESSES PESTICIDES IN THE EU?

THESE ARE THE KEY STEPS IN THE PROCESS:



EFSA

ECHA

EMA

OSHA

EEA

EU agencies

Environmental protection
legislation

il
s

Water

Waste

Slide courtesy of
Mounir Bouhifd



DG ENV

DG SANTE

European Com

specific chemicals
legislation

pharmaceuticals

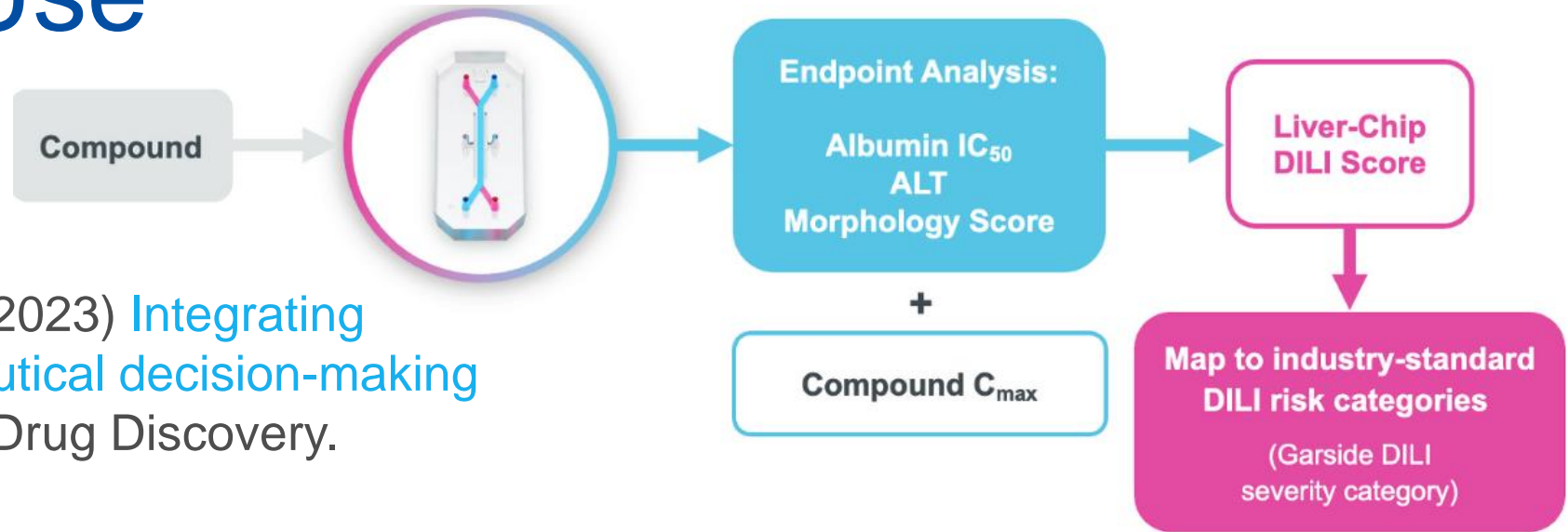
Pesticides

Biocides

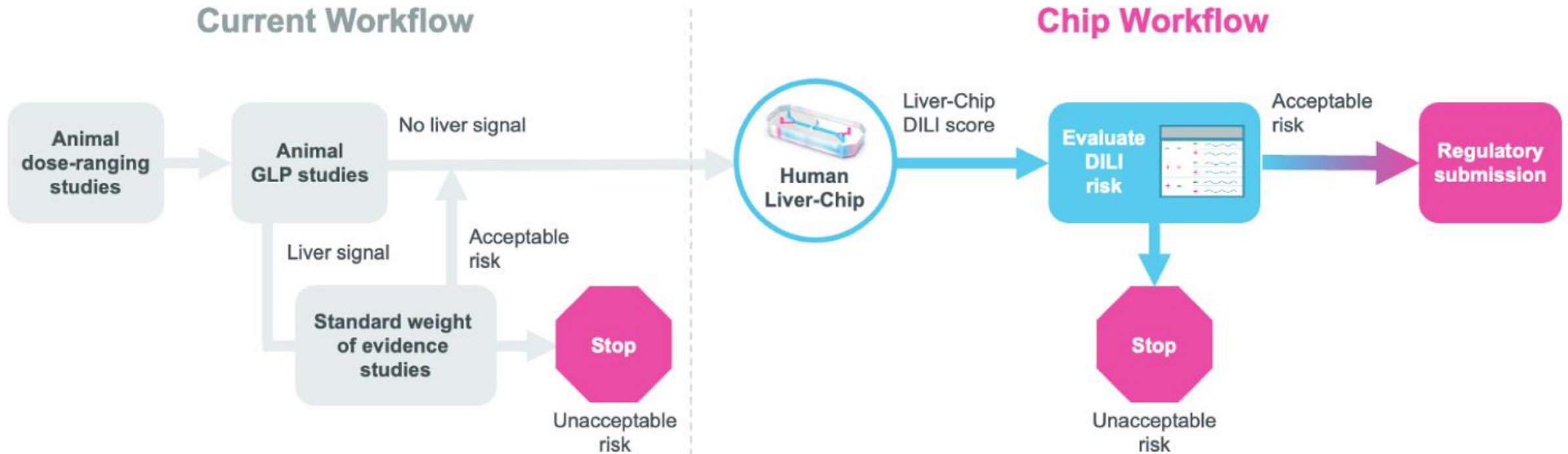


Implem

Context of Use in pharma



Daniel Levner & Lorna Ewart (2023) [Integrating Liver-Chip data into pharmaceutical decision-making processes](#), Expert Opinion on Drug Discovery.



Standardisation and information sources

International Guidelines

- Mutual Acceptance of Data
- Legal certainty & quality assurance
- Efficiency and harmonisation

Technical standards

- Multiple uses including validation
- Keep pace with NAM development
- Important role in innovation

Academic studies

- Bespoke tools and design
- Tackle specific problems
- Best practices influence quality

28-29 April 2021

Organ-on-chip

Putting Science into Standards



CEN-CENELEC
Focus Group on
Organ on chip

Stem Cell Reports
Meeting Report



OPEN ACCESS

Putting Science into Standards workshop on standards for organ-on-chip

Monica Piergiovanni,^{1,*} Ozlem Cangar,² Sofia B. Leite,¹ Livia Mian,³ Andreas Jenet,⁴ Raffaella Corvi,¹ Maurice Whelan,¹ Fabio Taucer,⁴ and Ashok Ganesh³

¹European Commission, Joint Research Centre (JRC), Ispra, Italy

²European Health and Digital Executive Agency (HaDEA), Brussels, Belgium

³CEN-CENELEC, Market Perspective and Innovation, Brussels, Belgium

⁴European Commission, Joint Research Centre (JRC), Brussels, Belgium

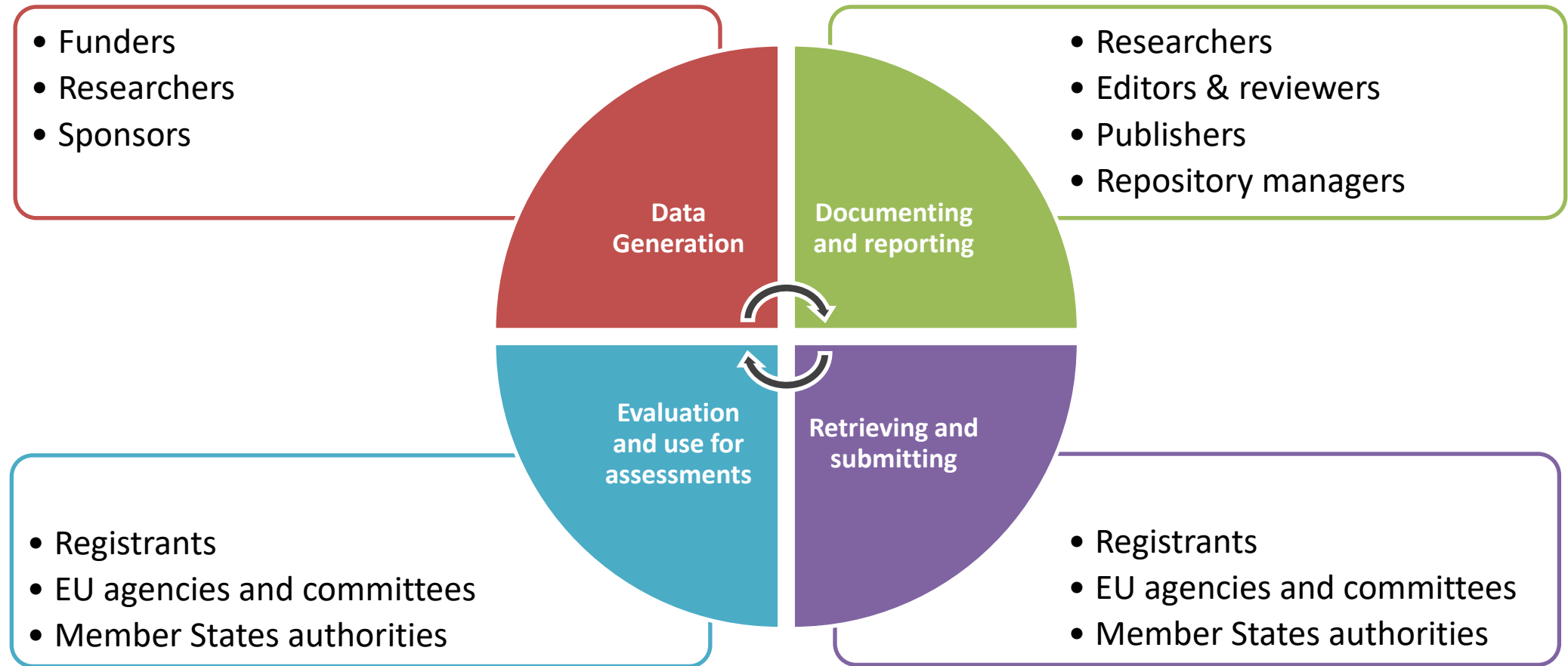
*Correspondence: monica.piergiovanni@ec.europa.eu

<https://doi.org/10.1016/j.stemcr.2021.07.010>

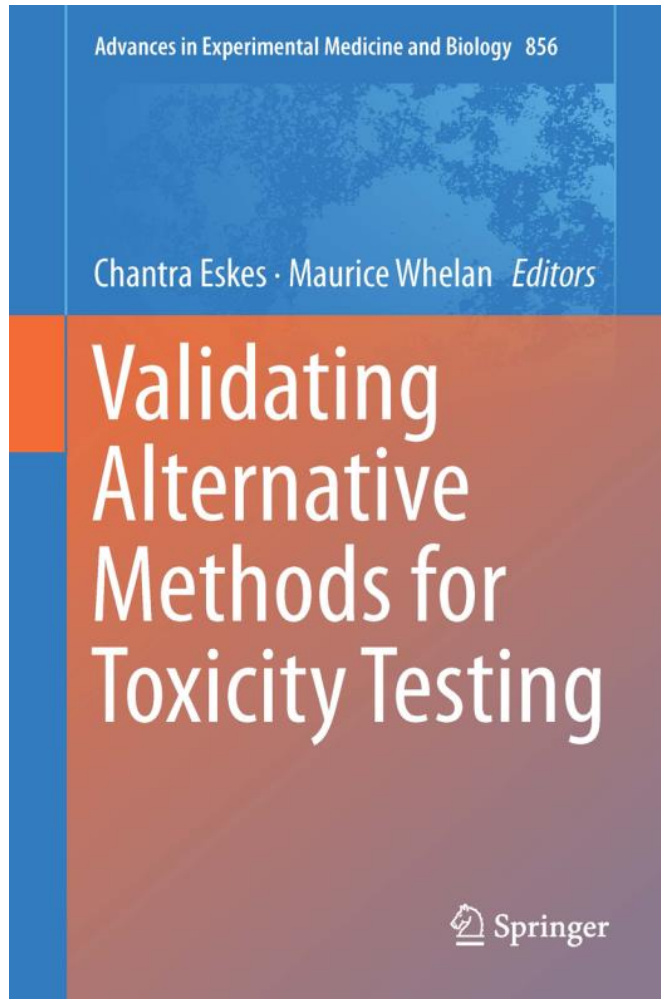
The European Commission Joint Research Centre and the European Standardization Organizations CEN and CENELEC organized the "Putting Science into Standards" workshop, focusing on organ-on-chip technologies. The workshop, held online on 28–29 April, 2021, aimed at identifying needs and priorities for standards development and suggesting possible ways forward.



Better use of academic data



Validation and qualification



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

3Rs Working Party Developing qualification criteria for Organ-on-Chip

WHAT
is needed

ECVAM workshop



HOW
to do it

WHO
does it

MPS WS, Berlin 2023



Unclassified

ENV/JM/MONO(2005)14

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

18-Aug-2005

OECD SERIES ON TESTING AND ASSESSMENT
Number 34

GUIDANCE DOCUMENT ON THE VALIDATION AND INTERNATIONAL ACCEPTANCE OF NEW
OR UPDATED TEST METHODS FOR HAZARD ASSESSMENT

**UNDER
REVISION**

Validation of 'thyroid disruptor' methods

- 14 **EU-NETVAL** labs
- 18 *in vitro* methods
- 12 developers
- Implement & optimise
- WL reproducibility
- Adhere to GIVIMP
- Data for IATA/DA



Developmental neurotoxicity

Assessment of pesticide active ingredients

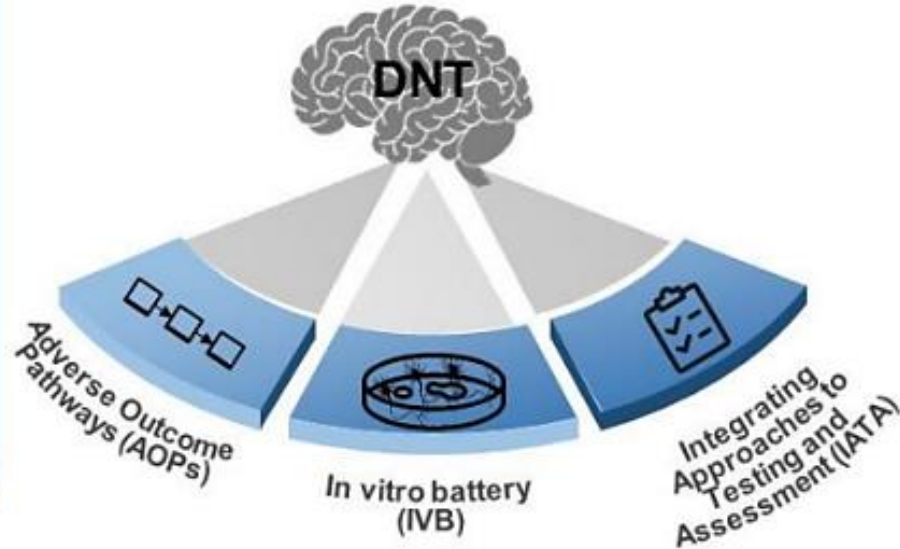
Highlights of work

- EFSA/OECD Workshop (Nov 2016)
- Formation of OECD DNT Expert Group (2017)
- Protocol for the implementation and interpretation of DNT in-vitro testing battery (November 2020)
- OECD DNT Guidance (first draft expected mid-2021)

Review

Toward a Better Testing Paradigm for Developmental Neurotoxicity: OECD Efforts and Regulatory Considerations

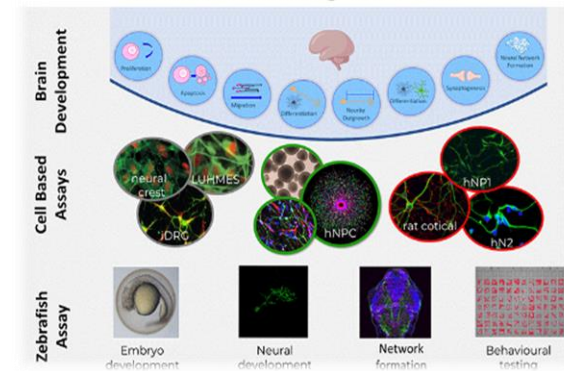
Magdalini Sachana ^{1,*}, Timothy J. Shafer ² and Andrea Terron ³



Main goals of the OECD DNT project

- Improve DNT testing
- Incorporate mechanistic knowledge
- Provide regulatory relevant examples through case studies
- Accelerate regulatory uptake of the DNT IVB

In vitro testing for DNT



EFSA JOURNAL

Scientific Opinion | Open Access | CC BY

Development of Integrated Approaches to Testing and Assessment (IATA) case studies on developmental neurotoxicity (DNT) risk assessment

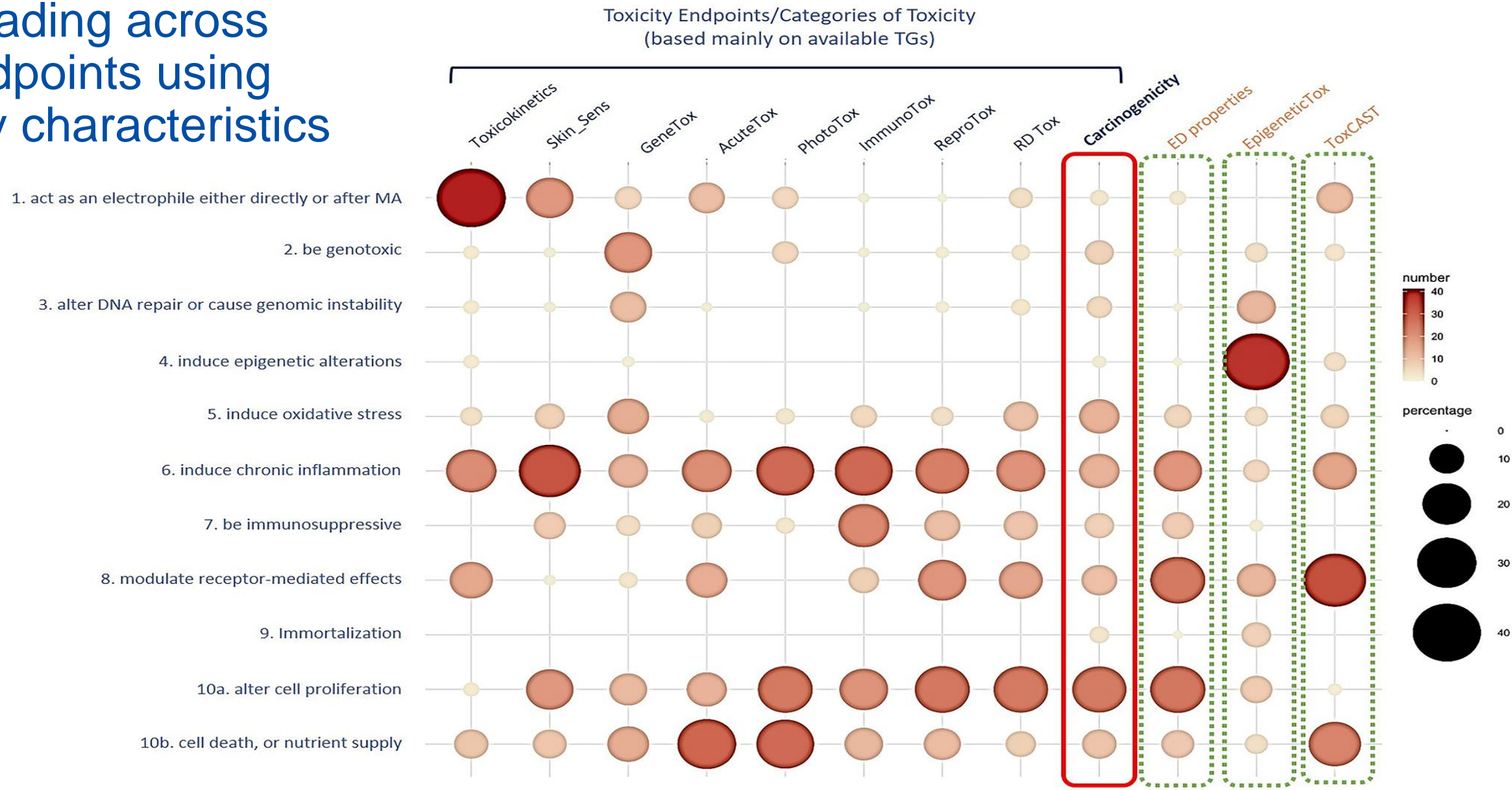


Initial recommendations on evaluation of in vitro data

<https://www.oecd.org/env/ehs/testing/developmental-neurotoxicity.htm>

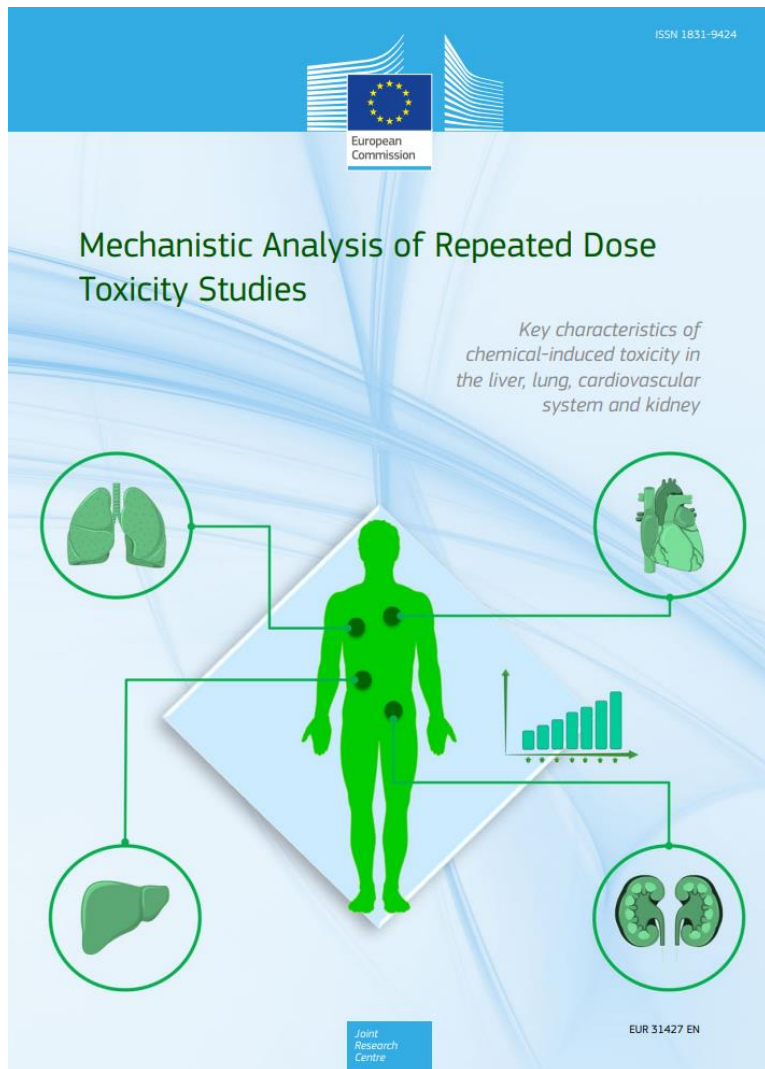


Reading across endpoints using key characteristics



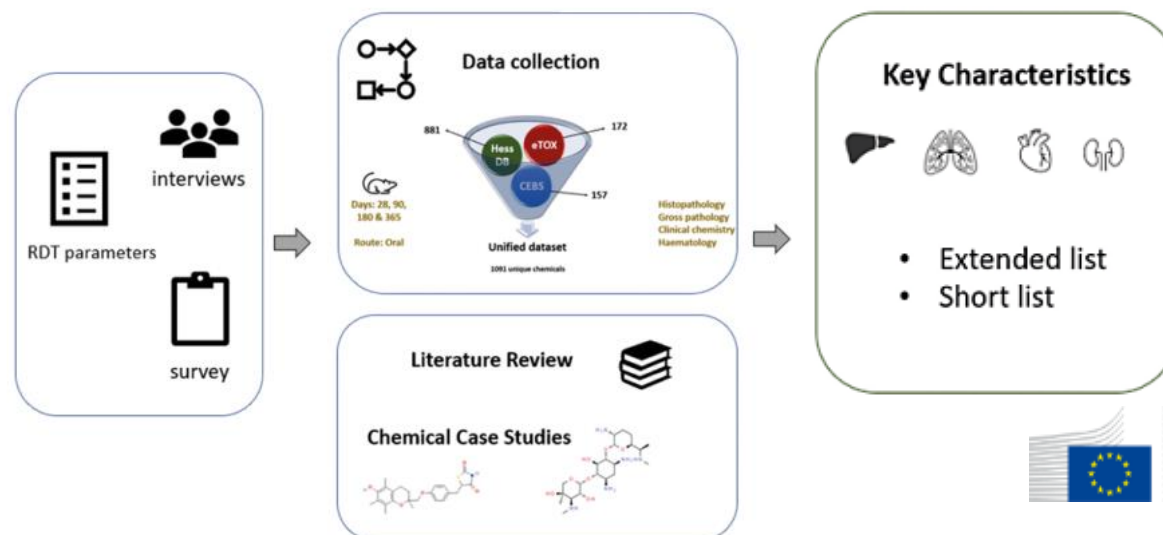
Madia et al. (2021) **Integration of data across toxicity endpoints for improved safety assessment of chemicals: the example of carcinogenicity assessment**, Arch Tox 95:1971–1993

Reverse engineering animal studies



OECD Test guideline	Type of study	Reference
407	28-day oral toxicity study (Rodents)	OECD, 2008
408	90-day oral toxicity study (Rodents)	OECD, 2018a
409	90-day oral toxicity study (Non-rodents)	OECD, 1998
410	28-day dermal toxicity study (Rat, rabbit or guinea pig)	OECD, 1981a
411	90-day dermal toxicity study (Rat, rabbit, or guinea pig)	OECD, 1981b
412	28-day inhalation toxicity study (Rodents)	OECD, 2018b
413	90-day inhalation toxicity study (Rodents)	OECD, 2018c
452	Chronic toxicity study (Rodents)	OECD, 2018d
453	Combined Chronic Toxicity/Carcinogenicity Studies (Rodents)	OECD, 2018e

Clinical observation	Clinical chemistry	Haematology	Pathology	Urinalysis
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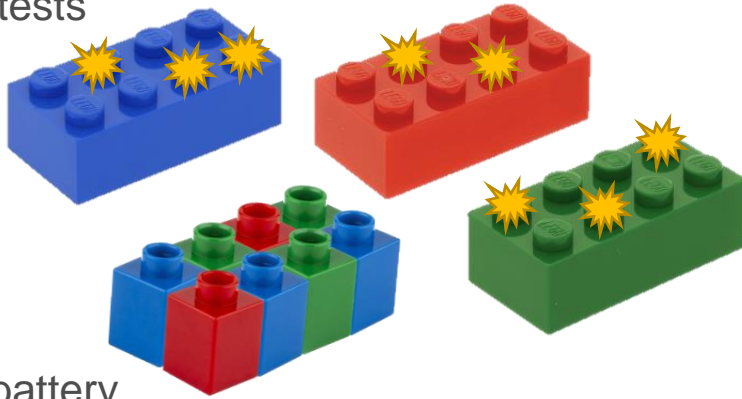
Optimised NAM based strategies

Regulatory Toxicology and Pharmacology 142 (2023) 105431

Towards a future regulatory framework for chemicals in the European Union – Chemicals 2.0

Elisabet Berggren, Andrew P. Worth *

Animal tests



NAM battery

		Activity (NAM-based toxicodynamics)		
		High	Medium	Low
Potential Systemic Availability (NAM-based toxicokinetics, based on ADME properties)	High	H	H	M
	Medium	H	M	L
	Low	M	L	L



On the EPAA web page



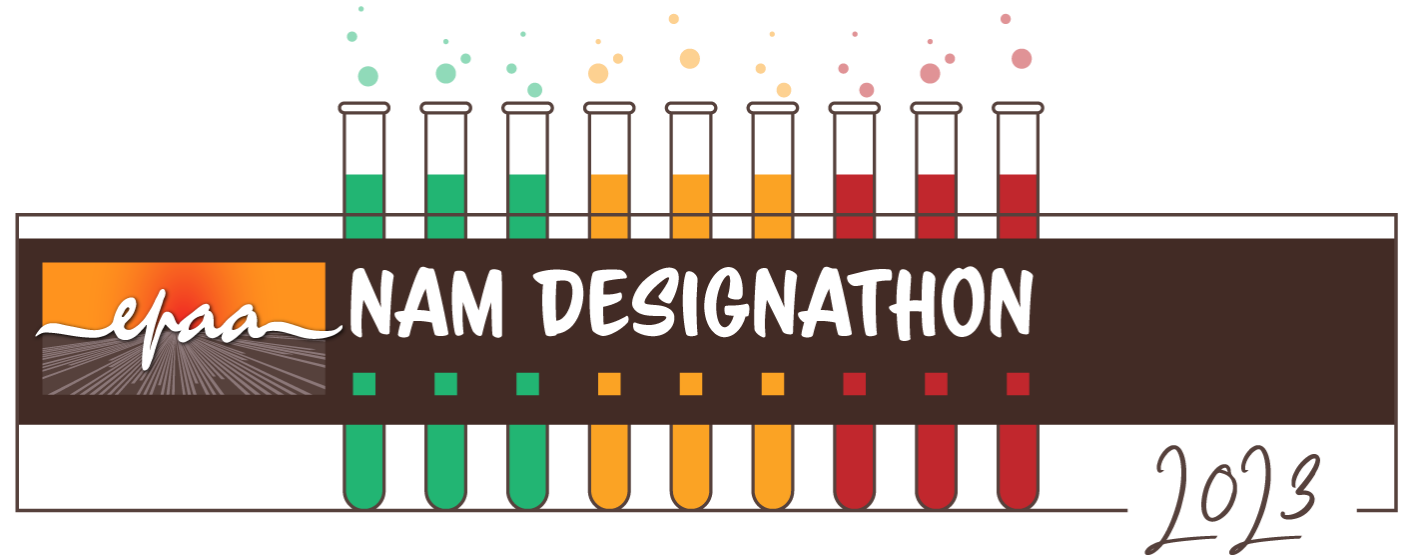
Register for pilot-phase and download chemical list & reporting template



Submit proposals by 31st Dec 2023



Workshop to discuss pilot-phase solutions with submitters (March 2024)



Thank you !

Maurice Whelan

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European Commission, Joint Research Centre (JRC).

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