Chemicals 2.0
can we make it better without using animals?

Elisabet Berggren, Joint Research Centre – European Commission

Webinar **NAM-based strategies for systemic toxicity assessment**, 12 March 2025

Joint Research Centre
Our purpose

The JRC provides independent, evidence-based knowledge and science, supporting EU policies to positively impact society.

What does science for policy?
Watch our video (https://www.youtube.com/embed/uF7uruvjAgg)

European Commission

Unit F3:
Systems Toxicology

EURL ECVAM

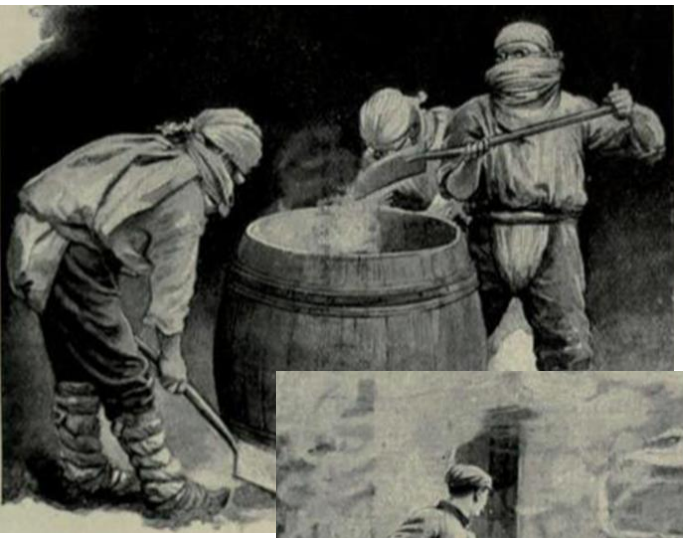
European Union Reference Laboratory for alternatives to animal testing

3Rs

mandate under Directive 2010/63

- research & evaluation
- validation
- dissemination
- promotion

European Commission



A history of efforts to protect human health and the environment from dangerous chemicals has stepwise built our current safety management of chemicals

Chemicals Management within the EU

Regulation 1907/2006 on registration, evaluation, authorisation and restriction of chemical substances **'REACH'**

Regulation 1107/2009 on the placing of **Plant Protection Products** on the market

Regulation 528/2012 on authorisation of **Biocidal** active ingredients and **Products**

Regulation 1272/2008 on classification, labelling and packaging of chemical substances and mixtures **'CLP'**

Directive 2001/82/EC on **Veterinary Medicinal Products**

Directive 2001/83/EC on **Human Medicinal Products**

Regulation 1223/2009 on **Cosmetic Products**

Directive 2004/37/EC on **carcinogens, mutagens or reprotoxic substances at work**

Directive 2009/48/EC on **the safety of toys**

EU chemicals acquis: >40 pieces of legislation

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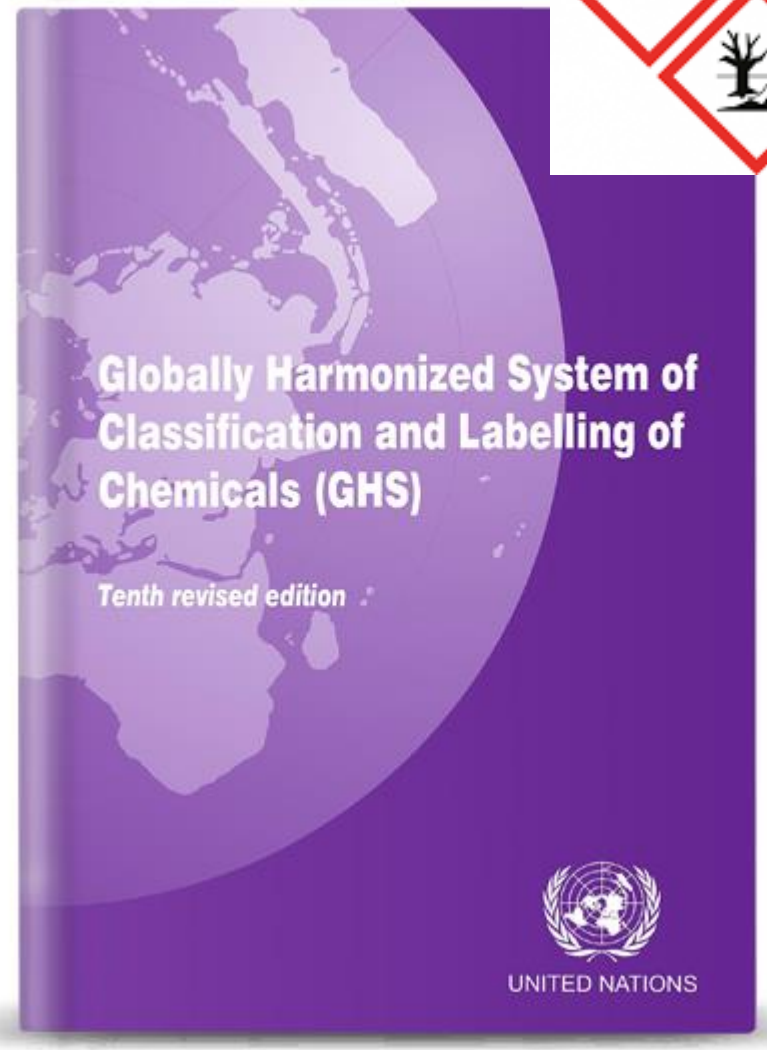

1.3.2.4.6 Animal welfare

The welfare of experimental animals is a concern. This ethical concern includes not only the alleviation of stress and suffering but also, in some countries, the use and consumption of test animals. Where possible and appropriate, tests and experiments that do not require the use of live animals are preferred to those using sentient live experimental animals.

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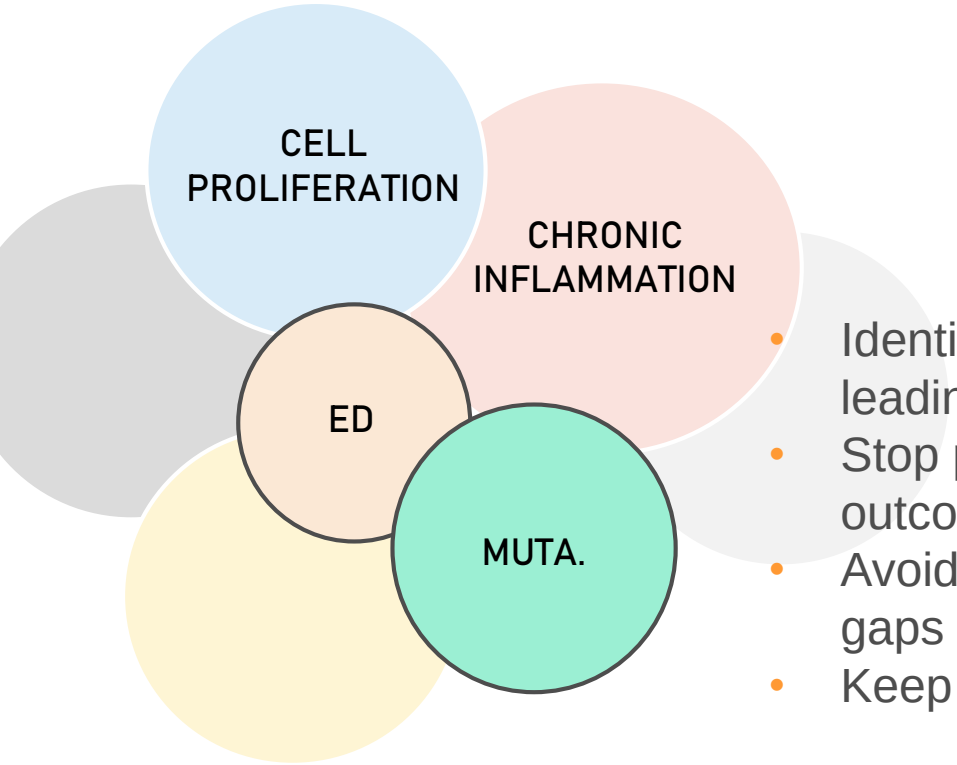
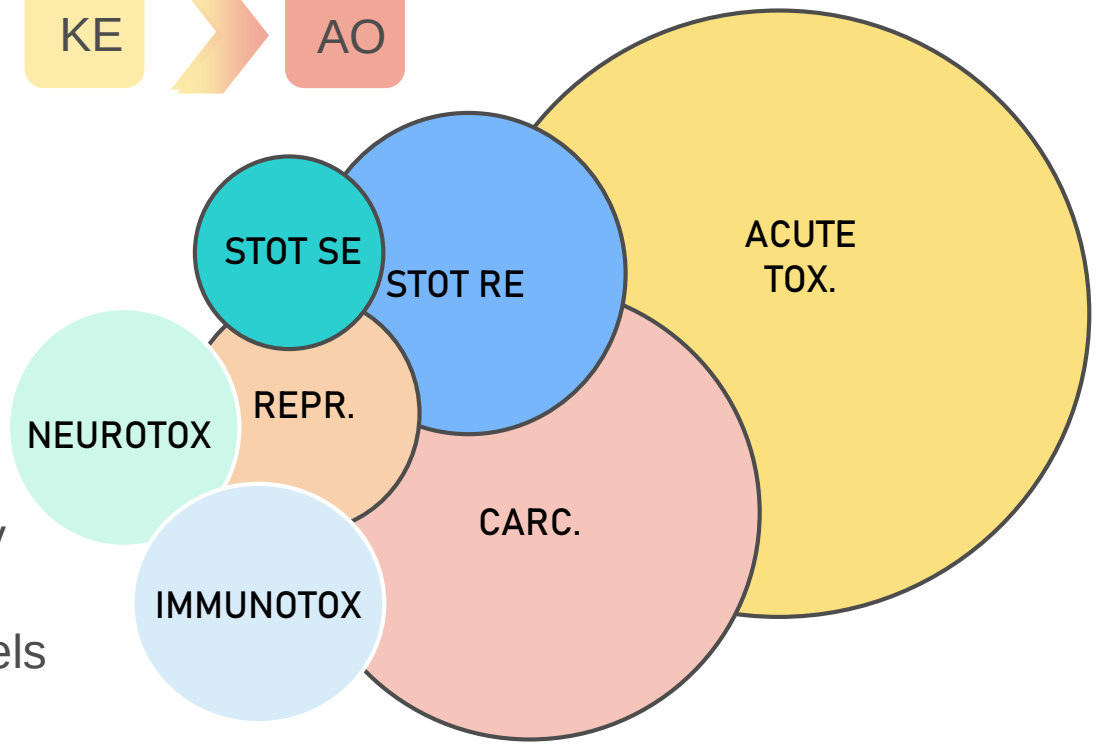
Overlaps between human systemic hazard classes in current EU harmonized classifications

	TOTAL NUMBER CHEMICALS CLASSIFIED IN THIS CLASS	CHEMICALS ONLY IN THIS CLASS AMONG THE CLASSES RELEVANT TO SYSTEMIC TOXICITY	CHEMICALS CLASSIFIED AT LEAST IN ONE OTHER CLASS RELEVANT TO SYSTEMIC TOXICITY	OVERLAP OF CHEMICALS CLASSIFIED SPECIFIED BY CLASS					
				MUTAGENICITY	CARCINOGENICITY	REPRODUCTIVE TOXICITY	STOT-RE	STOT-SE	ACUTE TOXICITY
MUTAGENICITY	575	18 (3%)	557 (97%)	-	517 (90%)	76 (13%)	88 (15%)	18 (3%)	118 (21%)
CARCINOGENICITY	1151	387 (34%)	764 (66%)	517 (45%)	-	121 (11%)	171 (15%)	58 (5%)	264 (23%)
REPRODUCTIVE TOXICITY	388	96 (25%)	292 (75%)	76 (20%)	121 (31%)	-	163 (42%)	33 (9%)	199 (51%)
STOT-RE	552	74 (13%)	478 (87%)	88 (16%)	171 (31%)	163 (30%)	-	43 (8%)	372 (67%)
STOT-SE	297	113 (38%)	184 (62%)	18 (6%)	58 (20%)	33 (11%)	43 (14%)	-	161 (54%)
ACUTE TOXICITY	1703	985 (58%)	718 (42%)	118 (7%)	264 16%)	199 (12%)	372 (22%)	161 (9%)	-



- Identify intermediate effects leading to adverse outcome
- Stop predicting adverse outcome
- Avoid redundancy & identify gaps upstream
- Keep current protection levels



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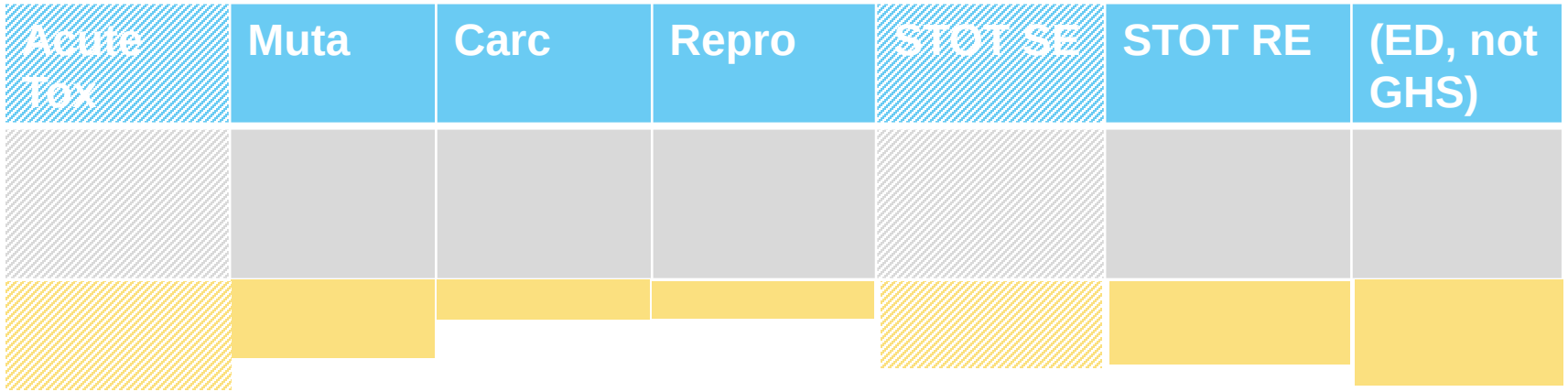
GHS & SYSTEMIC HEALTH EFFECTS



Current criteria based on human evidence and animal methods

Criteria based on non-animal methods increases with time

CAN WE CREATE **ONE SIMPLIFIED, MORE FLEXIBLE AND LESS COMPLEX HAZARD CLASS** COVERING ALL SYSTEMIC TOXICITY CONCERNS WITH CRITERIA ONLY BASED ON NON-ANIMAL METHODS?

Systemic Toxicity

*Criteria only based on non-animal methods, overlapping but not identical to the non-animal criteria introduced under the current classes, **but more importantly providing same protection level as the other classes combined***

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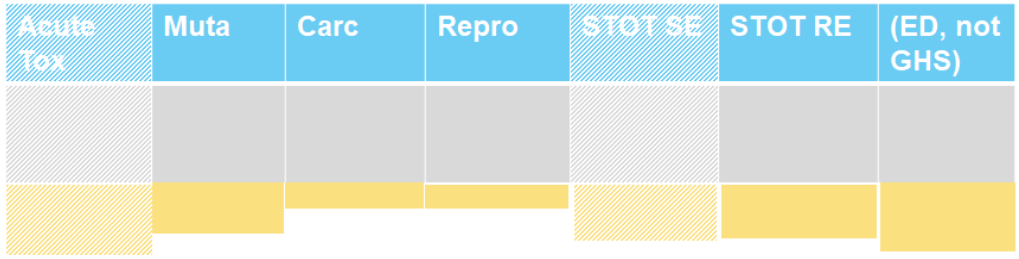
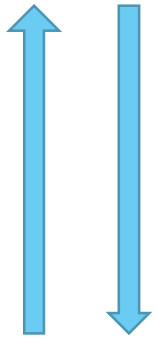
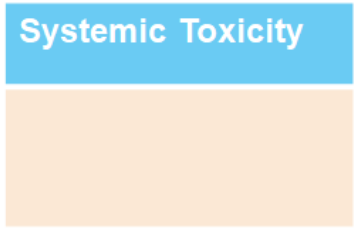
FROM ANIMAL-BASED CRITERIA TO NON-ANIMAL BASED CRITERIA



Continuous mutual exchange of progress in non-animal methodologies during parallel development of the existing classes and the new additional common animal-free class





Criteria based on human evidence and animal methods will remain to avoid obligation to re-evaluate already classified chemicals and allow for use of existing data

Criteria based on non-animal methods increase, as pushed into the system step by step

- *to provide partial replacement,*
- *to strengthen weight of evidence considerations,*
- *to cover additional health concerns*

Criteria based only on non-animal methods are developed on evidence from bio-activity and systemic availability, respecting the concept of equal protection gained by calibrating the system with already classified chemicals.

Non-animal methods are pulled into the system, as more reliable and relevant methods, providing an added value, become availble.

Regulatory Toxicology and Pharmacology 142 (2023) 105431

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

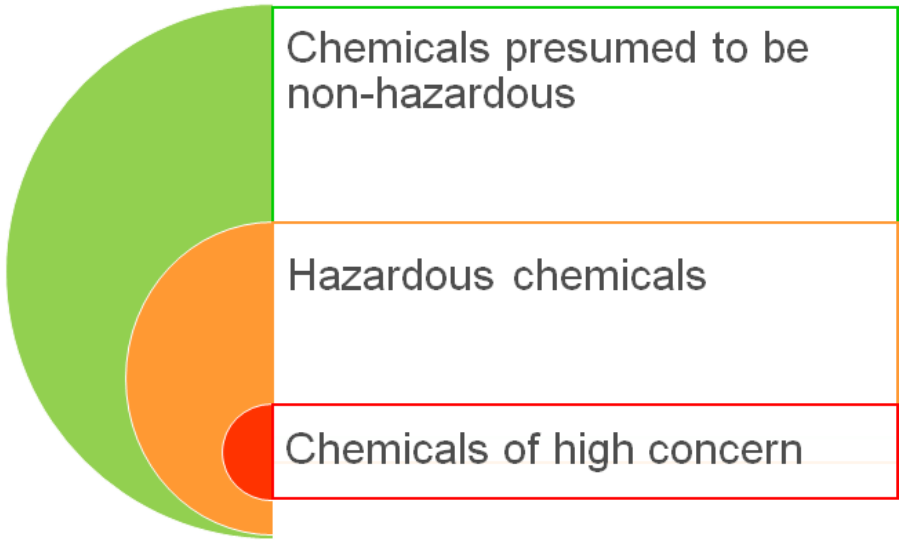
journal homepage: www.elsevier.com/locate/yrtph

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

Elisabet Berggren, Andrew P. Worth *

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

PRINCIPLE OF EQUIVALENT PROTECTION:
MAKE THE SAME DECISIONS, NOT NECESSARILY THE SAME PREDICTIONS



→ Innovate
→ Use without restriction

→ Restrict via concentration limits
→ Demonstrate safe use

→ Ban for some or all uses

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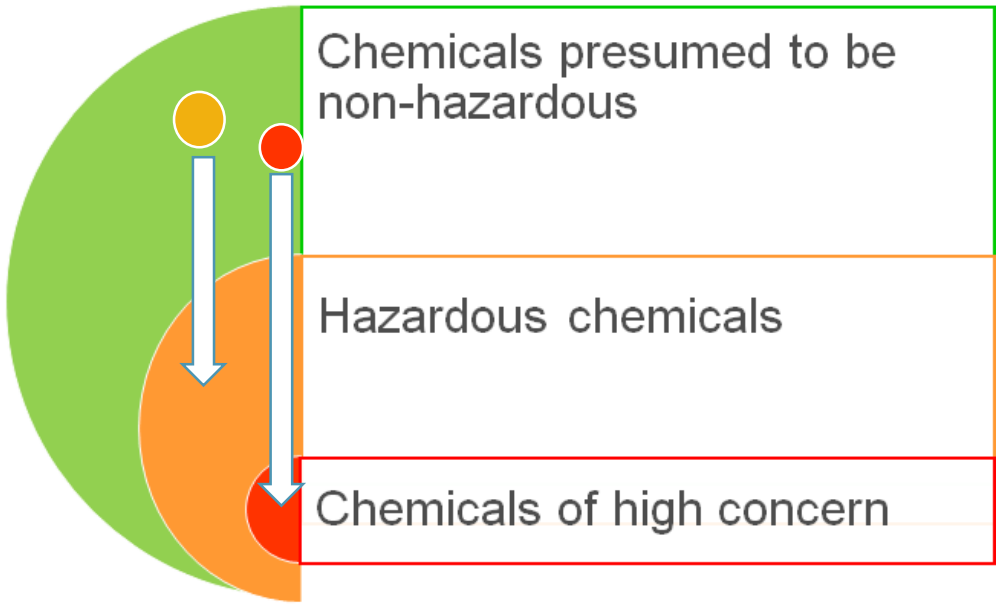
DEVELOPING A NEW CLASSIFICATION SCHEME

- A generic risk matrix is developed to assign chemicals to groups 1-3 (low, medium & high concern)
- Existing data for already classified chemicals (high & medium concern) are used to calibrate the classification scheme resulting in **equivalent protection**

		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

NAMs CAPTURE CHEMICALS CURRENTLY TREATED AS GREEN, BUT BASED ON NO OR LIMITED INFORMATION

- Application of the new classification scheme to chemicals in the current low concern group will result in some additional classifications and thus an **overall higher level of protection**

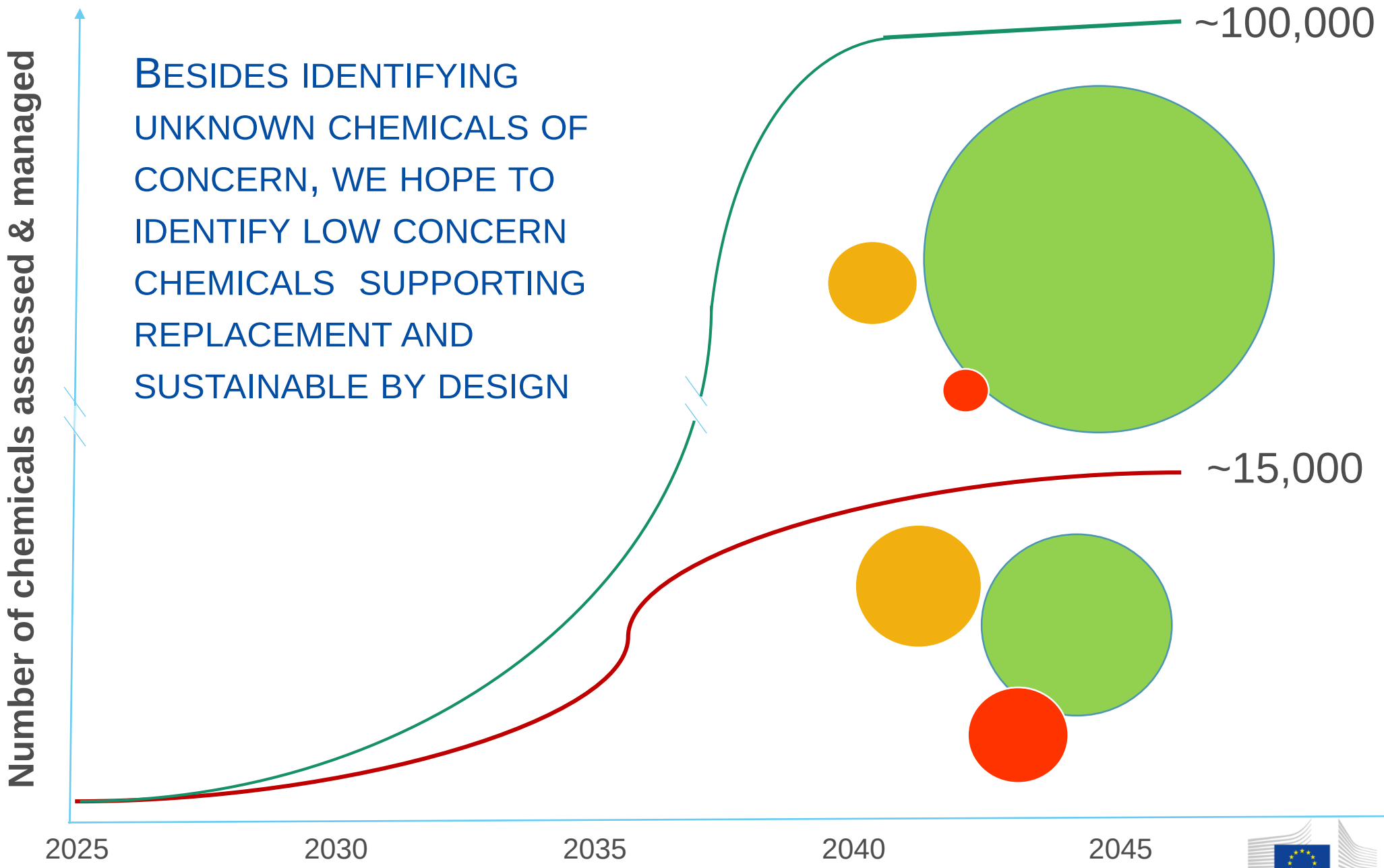


→ Demonstrate safe activity/systemic availability profile

→ Classification & Labelling +
→ Risk assessment

→ Classification & Labelling

BESIDES IDENTIFYING UNKNOWN CHEMICALS OF CONCERN, WE HOPE TO IDENTIFY LOW CONCERN CHEMICALS SUPPORTING REPLACEMENT AND SUSTAINABLE BY DESIGN



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https://single-market-economy.ec.europa.eu/calls-expression-interest/epaa-designathon-human-systemic-toxicity_en

The European Partnership for Alternative Approaches to Animal Testing (EPAA) aims to replace animal testing by innovative, non-animal testing methods.

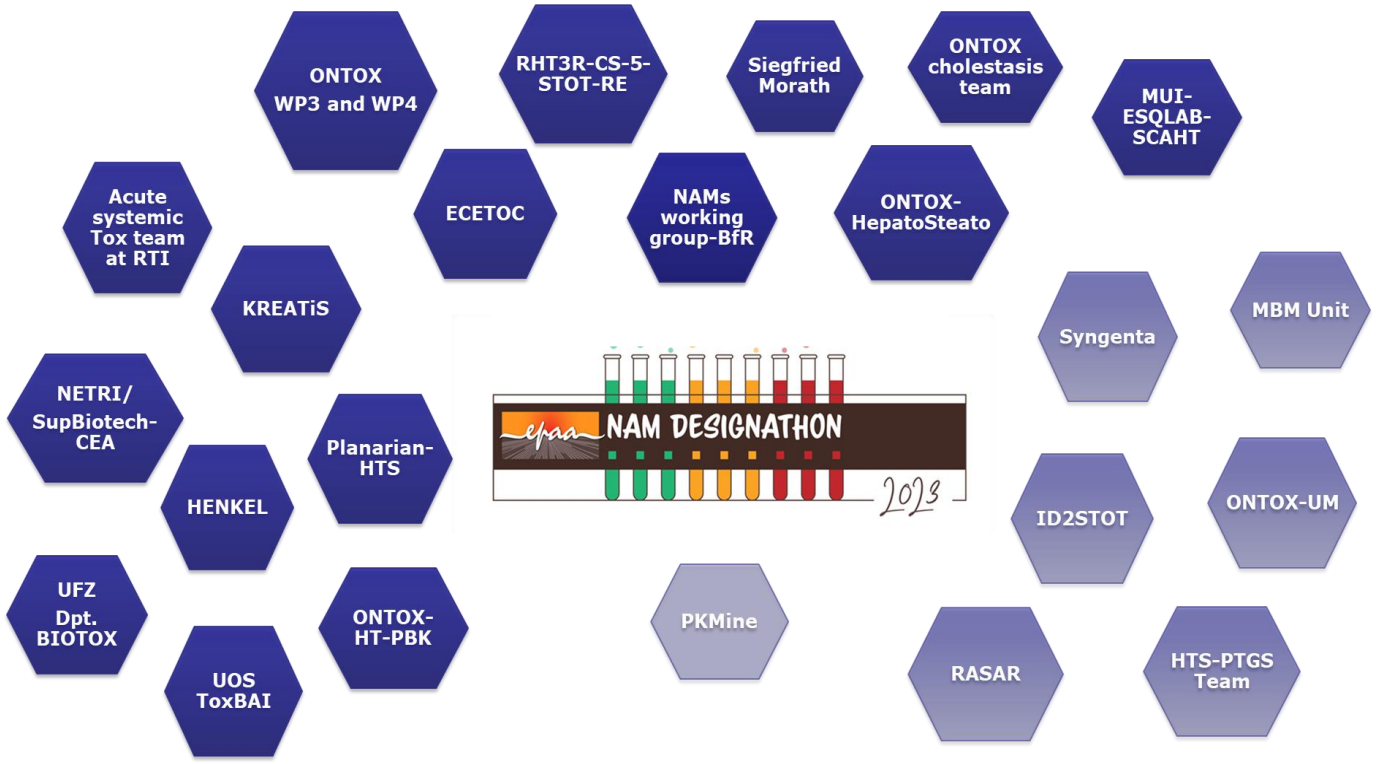
The EPAA includes 5 Directorates-General of the European Commission, 39 companies, and 9 European industry federations, representing 8 industrial sectors.

EPAA Designathon – the pilot phase

		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

Clear objectives linked to an intended outcome and aligned with strategic goal

Innovative challenge & prototype NAM-based solutions



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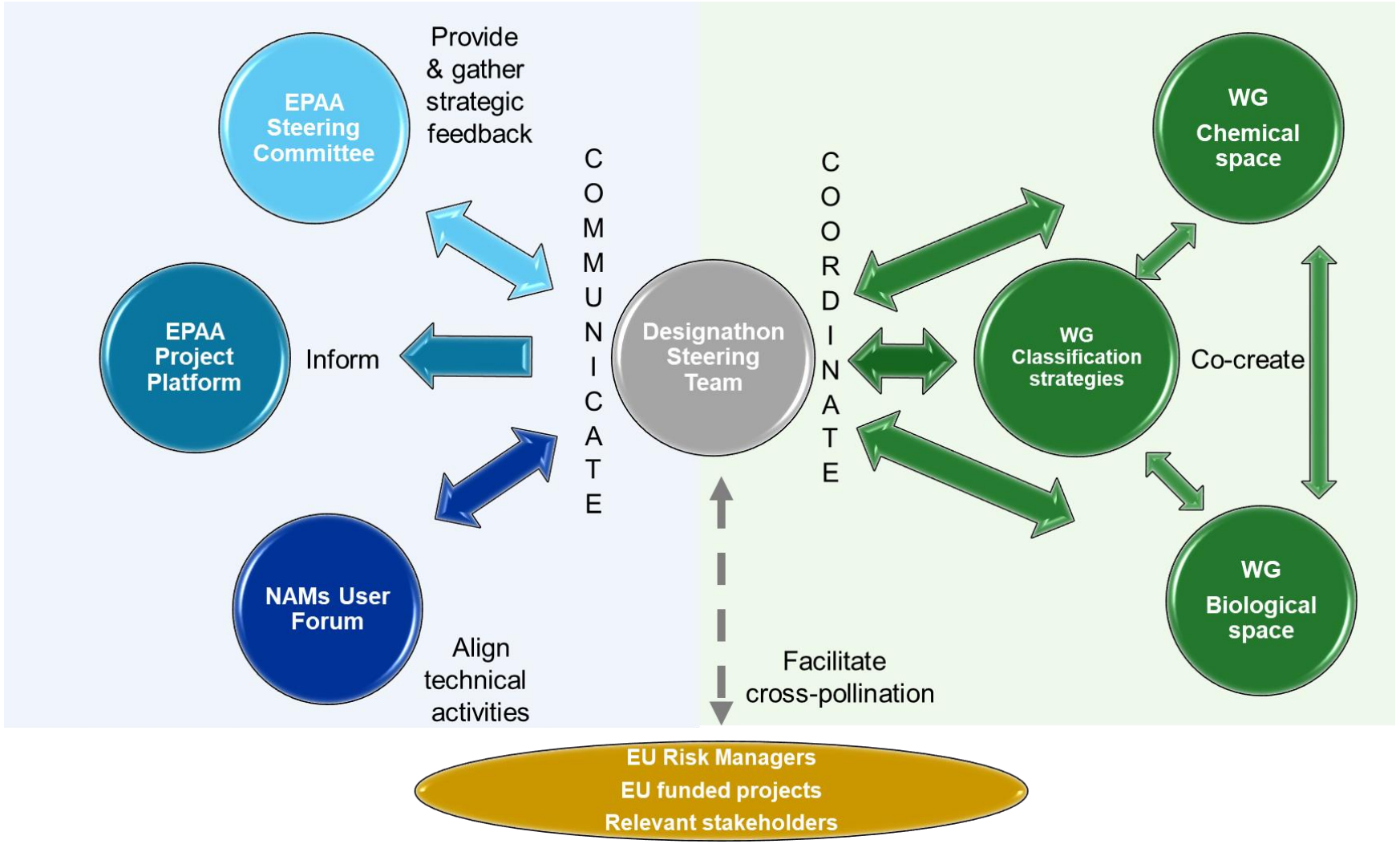
EPAA Designathon – co-creation phase



Cross-disciplinary collaboration

Co-creation of solutions

Stakeholder engagement & feedback

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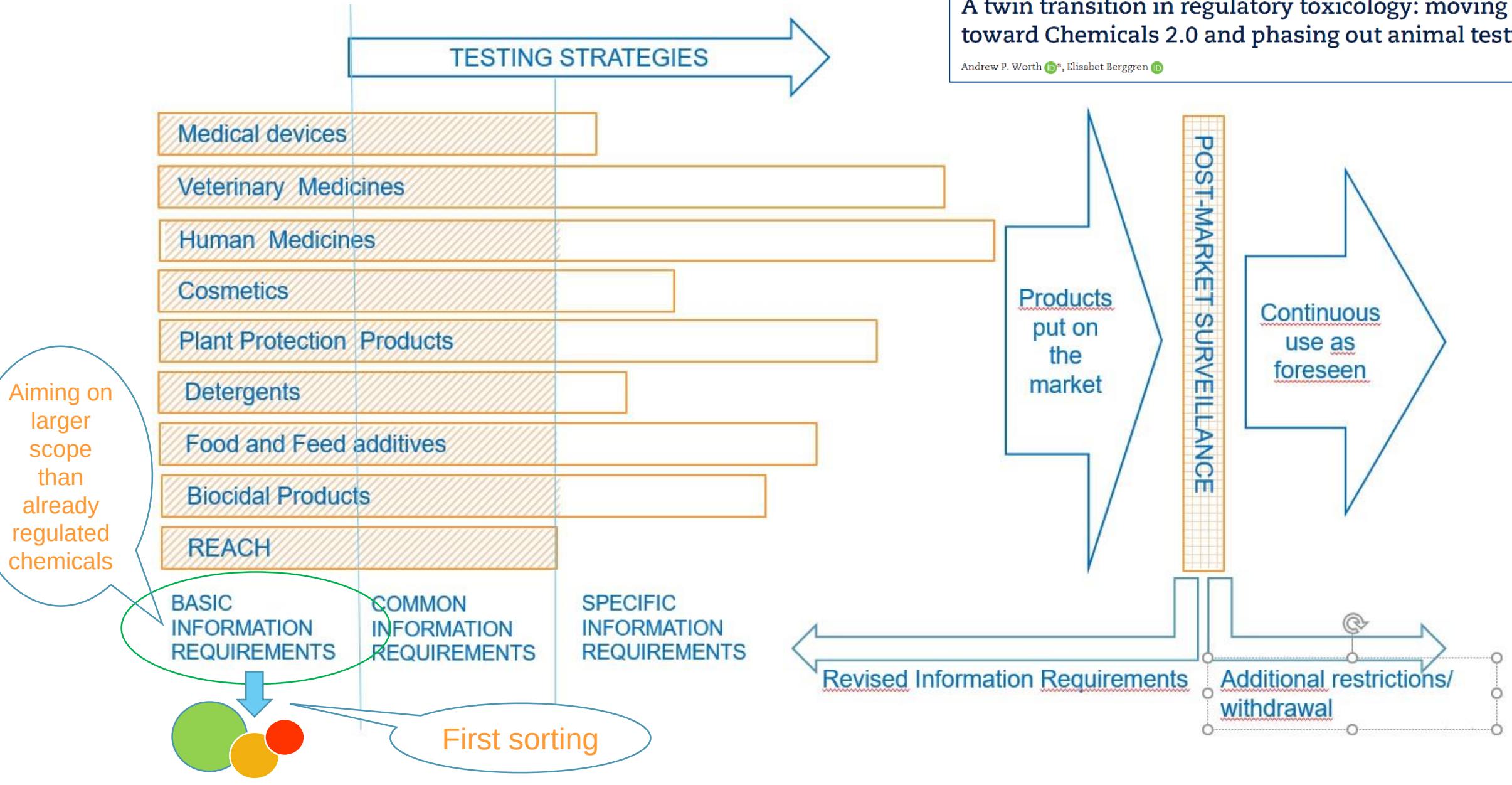
INFORMATION REQUIREMENTS IN EU CHEMICAL LEGISLATION

OXFORD SOT Society of Toxicology academic.oup.com/toxsci
Toxicological Sciences, 2024, 1–6
https://doi.org/10.1093/toxsci/kfae130
Advance Access Publication Date: October 3, 2024
Forum

A twin transition in regulatory toxicology: moving toward Chemicals 2.0 and phasing out animal testing

Andrew P. Worth*, Elisabet Berggren



Risk Assessment & the Principle of Equivalent Protection

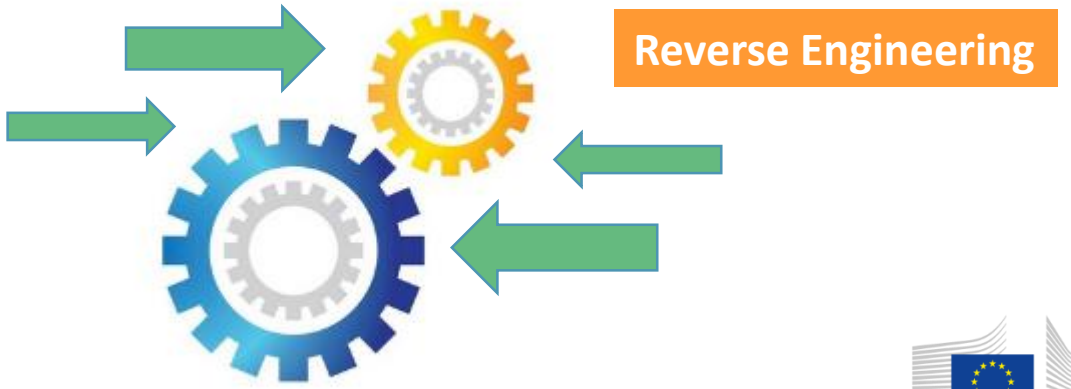
- Group chemicals based on their current risk management measures – **risk categories**
- Identify relevant physicochemical, NAM-based toxicokinetic/dynamic and possibly use-related properties
- Identify a quantitative measure of similarity - similarity metric (e.g. cut-off limits for certain properties)
- Decide a grouping algorithm for the properties and similarity metric to form the **risk categories**
- Group non assessed chemicals in risk categories and apply the corresponding risk management measures

Chemicals 2.0 and Why We Need to Bypass the Gold Standard in Regulatory Toxicology

Alternatives to Laboratory Animals
2024, Vol. 0(0) 1–5

DOI: 10.1177/02611929241296328
journals.sagepub.com/home/atl
Sage

Andrew P. Worth, Elisabet Berggren and Pilar Prieto



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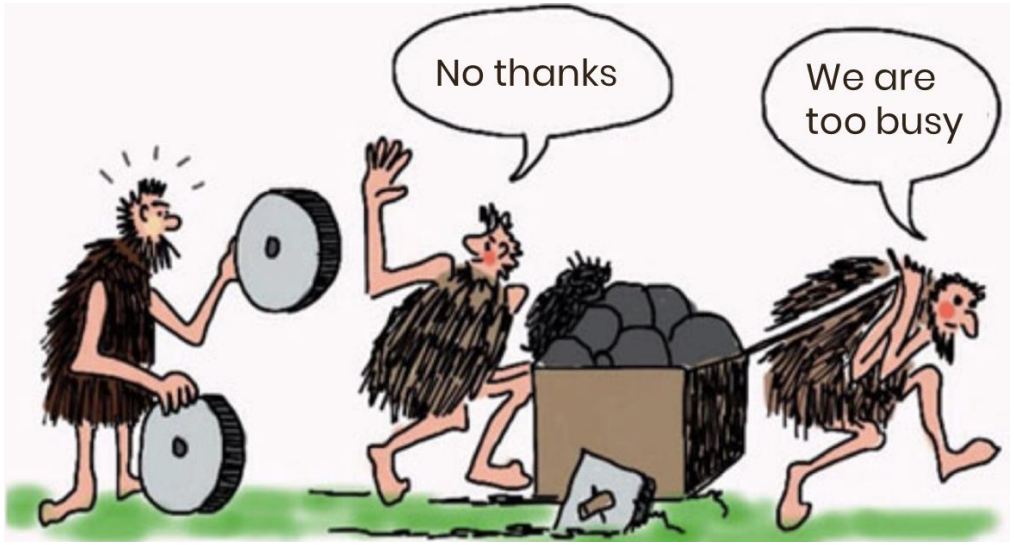
THE STATUS QUO BIAS – WE DO NOT LIKE CHANGE



Wellcome Open Research

Wellcome Open Research 2024, 9:167 Last updated: 02 SEP 2024

Check for updates

RESEARCH ARTICLE

REVISED **Chemicals regulation and non-animal methods: displacing the gold standard [version 2; peer review: 2 approved with reservations]**

Annamaria Carusi

Interchange Research, London, E5 8JW, UK

https://doi.org/10.12688/wellcomes.20581.2

PRECISIONTOX

D6.1 REPORT ON SOCIO-TECHNICAL BARRIERS TO THE UPTAKE OF NAMS

https://precisiontox.org/wp-content/uploads/2024/02/D6.1-Report-on-Socio-Technical-Barriers-26Jan.pdf

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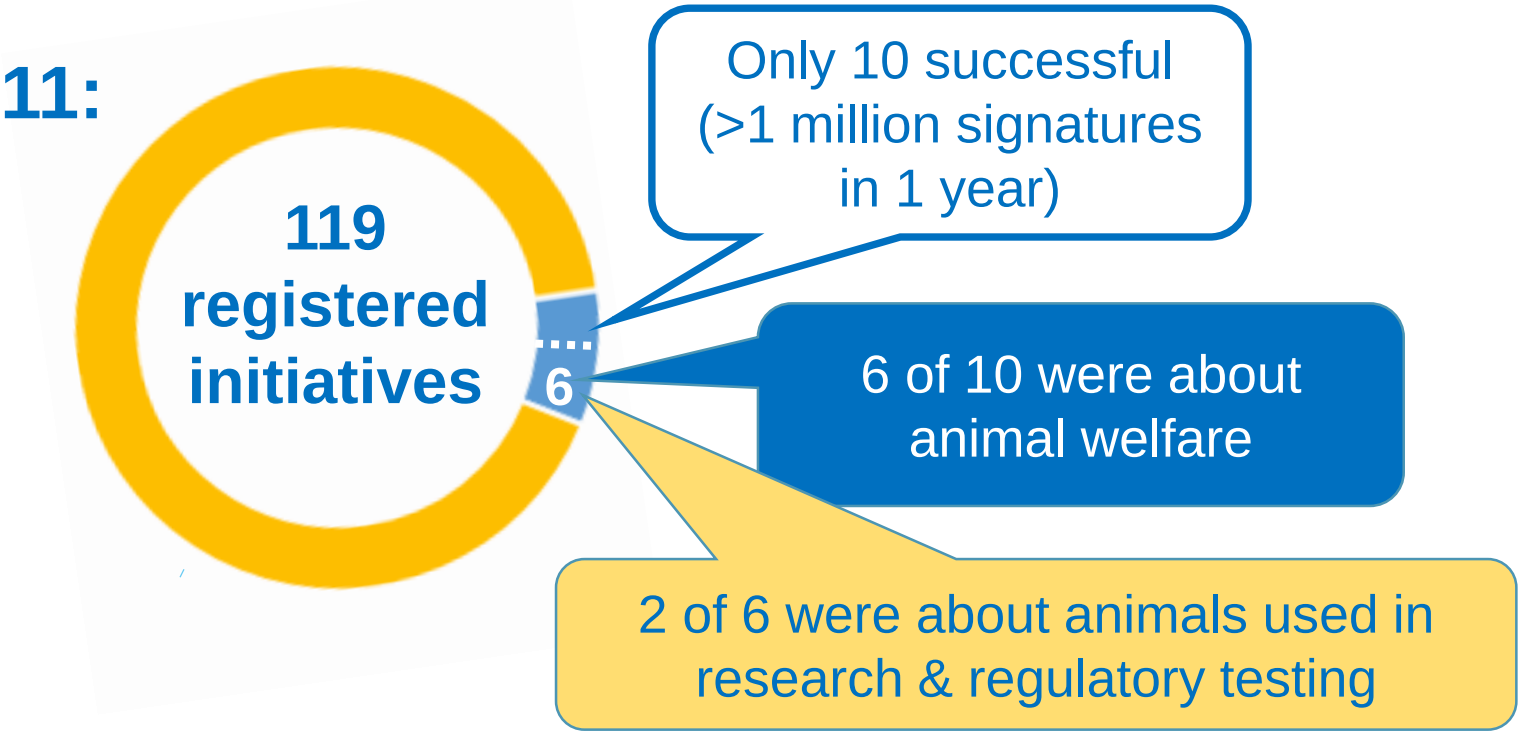
European Citizens' Initiative

Since 2011:



https://citizens-initiative.europa.eu/_en

Save Cruelty Free Cosmetics

1,217,916 signatures

- Commit to a Europe without Animal Testing

COMMISSION'S RESPONSE

1. Enforce the animal testing ban under the Cosmetics Regulation & clarify the interface between the Cosmetics and REACH Regulations

2. Kick off work on a **roadmap towards replacing animal testing in chemical safety assessments** involving all relevant stakeholders

3. Accelerate the reduction of animal testing in research, education and training & continue to support research on alternatives to animal testing with EU funding

Change Management Working Group – Tasks:

1. Introducing the concept of **transitional initiatives**
2. Developing **indicators** to monitor progress
3. Conducting **bilateral stakeholder discussions** to understand the incentives and concerns from their specific perspective
4. Proposing **collaboration models** to promote trust among stakeholders and develop confidence in non-animal assessment strategies

Scope:

- Informing & inspiring the roadmap construction
- Make the roadmap implementable

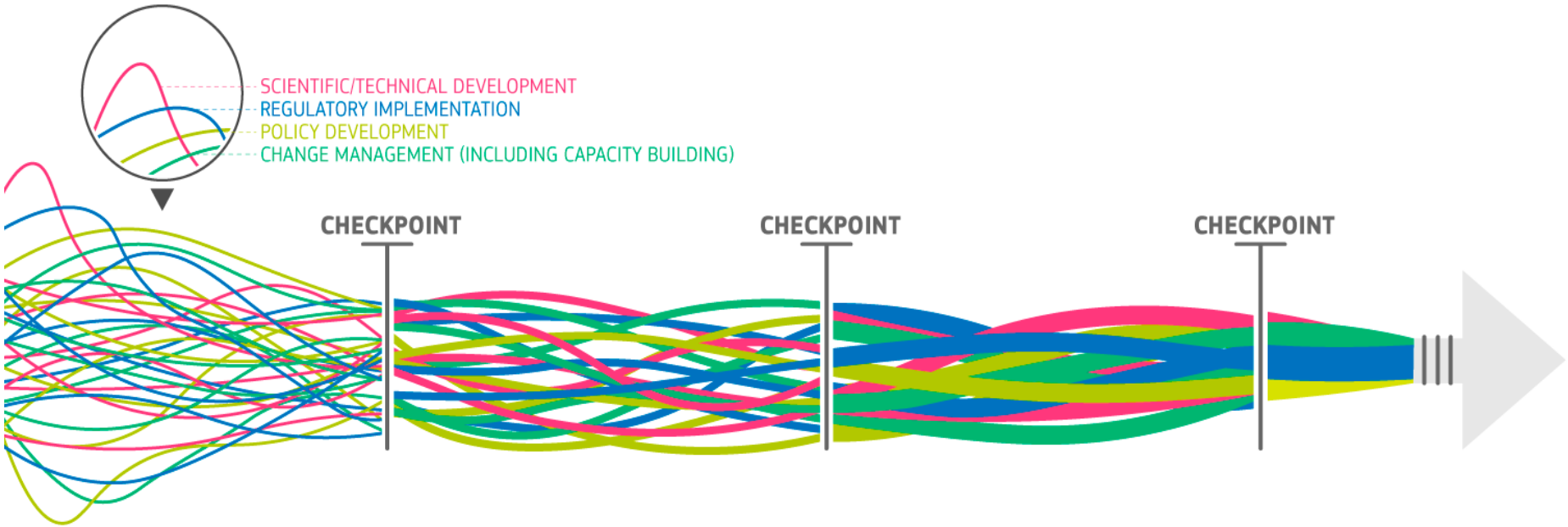
Transitional Initiatives – Units of Change

Initiative

A planned course of action including one or more activities, outputs and importantly, intended outcomes.

Transitional initiative

Any initiative contributing directly or indirectly to the replacement or reduction of animal use in regulatory assessments.



Confidence that chemicals are safe without animal testing

Thank you

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