Towards phasing out animal studies

Tomasz Sobański

Computational Assessment and Alternative Methods Unit, ECHA

tomasz.sobanski@echa.europa.eu

Andrea Terron

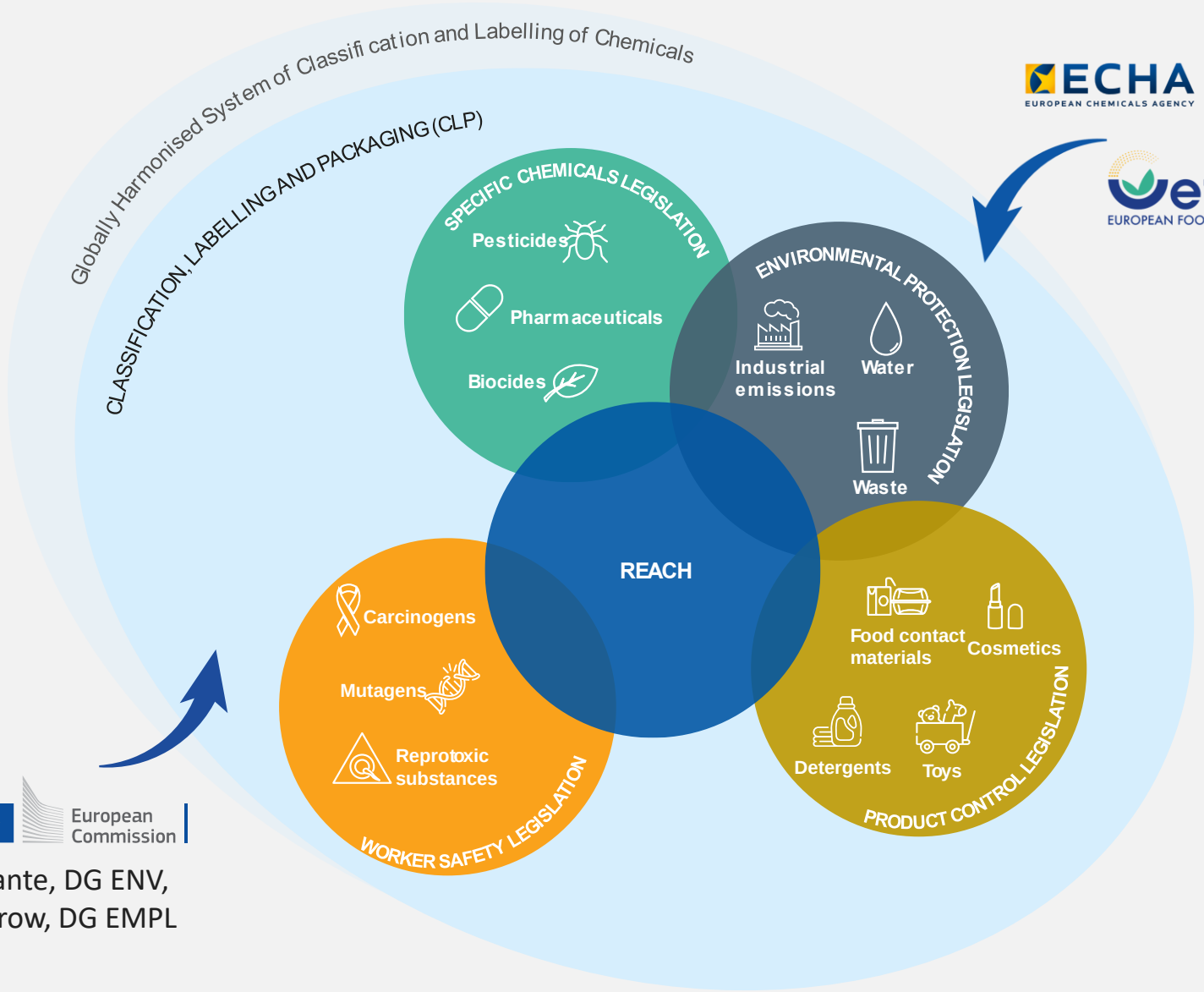
Mammalian tox, Pesticide Peer Review Unit, EFSA

andrea.terron@efsa.europa.eu

ECHA EUROPEAN CHEMICALS AGENCY

efsa EUROPEAN FOOD SAFETY AUTHORITY

Landscape of the EU's chemicals legislation



ECHA EUROPEAN CHEMICALS AGENCY

EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

efsa EUROPEAN FOOD SAFETY AUTHORITY

European Environment Agency

European Agency for Safety and Health at Work

European Commission

DG Sante, DG ENV,
DG Grow, DG EMPL

ECHA EUROPEAN CHEMICALS AGENCY | efsa EUROPEAN FOOD SAFETY AUTHORITY

Regulatory frameworks for chemicals in EU

Market Authorisation Systems (data rich)	Registration (license) systems	Market Notification Systems
Data rich, comprehensive risk assessments for market authorisation (pharmaceuticals, pesticides, biocides).	Hazard and risk assessment based on standard information requirements with link to CLP for generic risk management.	Risk assessment based on existing evidence, no explicit information requirements (Cosmetics).

Hazard identification and characterisation is the common root

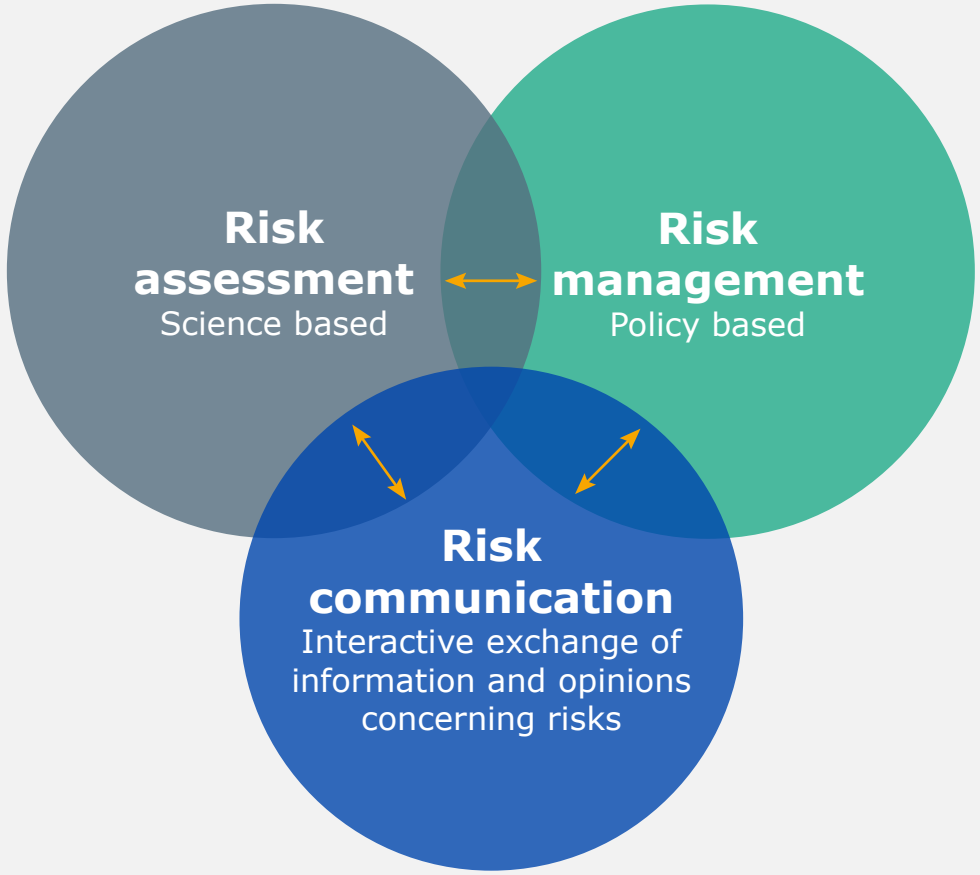
Hazard identification and characterisation primarily rely on animal studies

EFSA remit on risk assessment

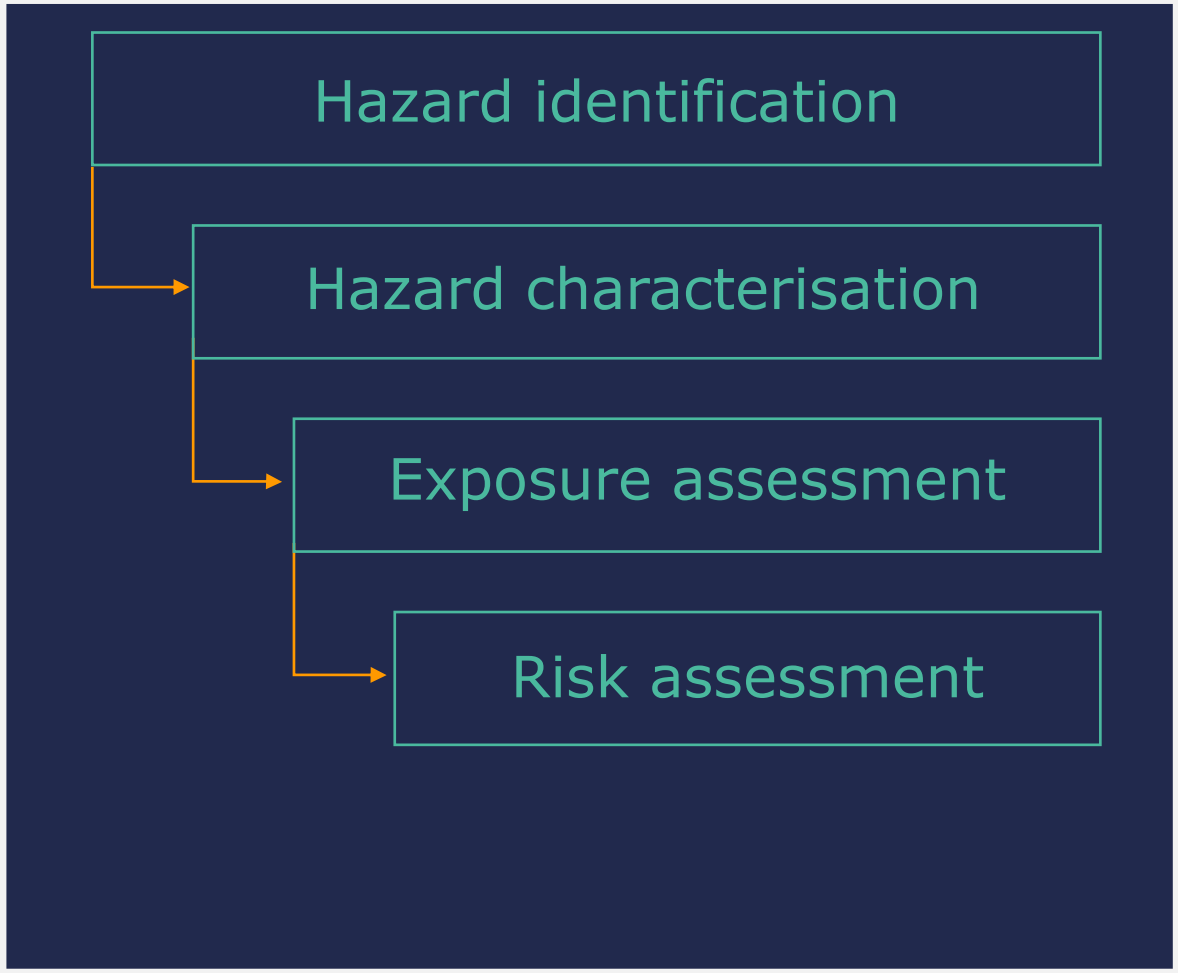
Regulated products (under EFSA remit) subject to a risk analysis and regulatory approval before entering EU market.

EFSA provides scientific advice to risk managers on any possible risk that the deployment of regulated products may pose to human health, animal health and the environment.

Decision on level of acceptable risk taken by risk managers who weigh policy options to accept, minimise or reduce characterised risks.



Place for new approach methodologies (NAMs) in risk assessment backbone



- In vivo hazard (e.g. brain weight) **vs**. NAM based hazard (e.g. decrease neurite length in human derived dopaminergic cells)
- Dose-response (NOAEL, LOAEL, BMD,) **vs**. concentration-response (ED 50, BMC, hit specific analytical pipeline)

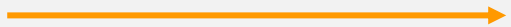
Point of departure

Complementary information:

- ADME characterisation
- Biokinetic data
- qIVIVE
- PBK modelling

Remark

Hazard data essential to define point of departure



No point of departure equals no risk assessment

Why use NAMs -EFSA perspective-

Fill data gap
(data and or methods not available)

- DNT
- Chronic NT
- Nanomaterial
- Pesticide metabolites
- Protein safety

Complementing existing data
(use of NAM in overall WOE)

- AOP informed IATA (submission of IATA case studies for DNT and NT)

Alternative to animal testing

- Impact on data requirements
- ADME-based phasing out dog studies for agrochemicals

ECHA EUROPEAN CHEMICALS AGENCY | efsa EUROPEAN FOOD SAFETY AUTHORITY

Lessons learnt

While phasing out animal testing following elements related to new test methods should be considered:

- ✓ **Identification of regulatory intended use or context of use**
- ✓ Target population
- ✓ Exposure conditions
- ✓ **Comparator analysis**
- ✓ **Outcome of interest**
- ✓ Strategy for regulatory implementation and validation
- ✓ Definition of fit for purpose
- ✓ **Key factors for uncertainty analysis**
- ✓ Cost
- ✓ Lab capacity
- ✓ **Scientific readiness**
- ✓ Timing
- ✓ Throughput
- ✓ Ethical considerations

ECHA’s reflections

Shifting away from animal testing

Starting point –REACH and CLP perspective-

Horizontal **generic approach** based on identification of **hazard**

→ Animal testing-free system should maintain main elements that function well:

Standard information requirements providing an input for:

- Classification and labelling (C&L)
- Reference doses for risk assessment

Defined hazard classes based on clear criteria

- Worldwide harmonisation via GHS
- With associated generic risk management measures (EU)

Quality data for decision making

- Linked to hazard classes
- Reliable, comparable and re-usable
- Allowing mutual acceptance of data (MAD)

Status

Currently we don’t have NAM solutions ready that cover these three main elements for systemic toxicity

Status

→ Replacing animal testing “one to one” successful for “simple” endpoints

- Takes time to develop robust and reliable predictions
- Requires harmonisation through OECD work on defined approaches

→ Replacing animal testing “one to one” challenging for “complex” endpoints

- Regulation relies on observed adversities
- New methods struggle to predict systemic adverse outcomes
- Standard requirements tied to specific animal tests
- Alternatives must assume full equivalence
- Comprehensive knowledge lacking for many regulatory endpoints

Proposed way forward

NAMs for animal-free hazard assessment in three steps:

Step 1. Define

Identify critical needs to transition to animal-free system to steer NAM development

Step 2. Demonstrate

Apply already available NAMs under current system

Step 3. Re-design

Re-think overall system to enable NAMs and **redefine** main elements

ECHA EUROPEAN CHEMICALS AGENCY | efsa EUROPEAN FOOD SAFETY AUTHORITY

Step 1: identify (and address) critical needs

Demonstrate NAMs can derive protection levels comparable with current ones

1 Hazard identification

Ability to demonstrate NAMs, (e.g. an integrated in vitro/in silico system) can be used to allow conclusive outcome on (lack of) hazardous properties for given regulatory endpoint

2 Hazard characterisation

Ability to reliably identify hazard based on changes at molecular/cellular level instead of observed adversity in an organism

3 Extrapolation

Ability to reliably convert concentrations directly measured or predicted by NAMs into external doses used to set safety levels, to communicate hazard and assess risks

Step 2: Demonstrate

Apply NAMs under current system to build experience and gain confidence

ECHA is currently focusing on this step as already now there is significant potential for **refinement** and **reduction**, using tools already available in the following areas:

→ Advancements in *in silico methods*:
- Enhanced predictive capacity and broader applicability from ECHA data efforts
- OECD QSAR Assessment Framework provides explicit regulatory acceptance criteria

→ Improved NAMs for read-across and grouping with clear acceptance criteria

→ Establishment of in vitro PBK/TK measurements and modelling for industrial chemicals

→ Integration of 'omics in regulatory toxicological testing for molecular data in relevant biological systems

Step 3: Re-design

Adapt overall system (if necessary)

While closing critical gaps identified in step 1 and gaining confidence in step 2, we can start considering what is needed for a new regulatory framework.

Potential areas for consideration are:

- → New system might not rely on the same regulatory endpoints as we know them today
- → How to derive reference values for risk assessment from molecular data (not adverse effects)
- → How to calibrate the system against expected and well-defined protection goals
- → Revision of CLP criteria to make them more suitable for non-animal methods
- → Throughput/performance and cost optimisation
- → Revision of the validation system

Need for faster validation of the new test methods

→ Current validation system for new test methods:

- Scientific and technical readiness assessment (measuring relevant features reproducibly and interpretably)
- Evaluation of regulatory implementation readiness (SOP, QC, transferability)
- Assessment of regulatory suitability (relevance for assessing hazards)

→ For more complex tox endpoints such schema is not directly applicable as there is no animal free method allowing 1 to 1 replacement. Introduction of defined approaches is a step in good direction, but validation process is very resource intense and slow.

Need for reflection on how to modify validation process to make it faster and better suited for modern modular approaches.

There is a need for high quality building blocks (assays) which can be (re)used and combined to build solutions tailored to specific regulatory needs

ECHA EUROPEAN CHEMICALS AGENCY | efsa EUROPEAN FOOD SAFETY AUTHORITY

Joint conclusions

- → Need to develop methodology for deriving reliable reference values and information on the type of effects from molecular data
- → This methodology needs to be harmonised across sectors
- → Maintaining global harmonisation and mutual acceptance of data is essential
- → Need for confidence and capacity building for NAMs regulatory applications
- → Need for faster validation of new test methods to build extensive library of tools suitable for regulatory applications
- → Need for providing safe mechanisms for exchanging molecular data
- → Transition towards animal-free system will be a very complex process which will require strong commitment from all parties

Thank you

ECHA
EUROPEAN CHEMICALS AGENCY

efsa
EUROPEAN FOOD SAFETY AUTHORITY