

ROADMAP ACTIONS AND CHALLENGES IN PESTICIDES' ASSESSMENT - *EFSA'S VIEWS*

Sofia Batista Leite
Pesticides Peer Review Unit
Mammalian toxicology team

Maria Arena
PLANTS Unit
Team Ecotoxicology

EUROPEAN FOOD SAFETY AUTHORITY

AS WE SET THE SCENE

THE TRANSITION TO ANIMAL-FREE RISK ASSESSMENT

1



Animal-free Risk-assessment

Still not possible and will not be in a near future.

2



Protection assured

Assessment can change only when it ensures the same or a higher level of protection.

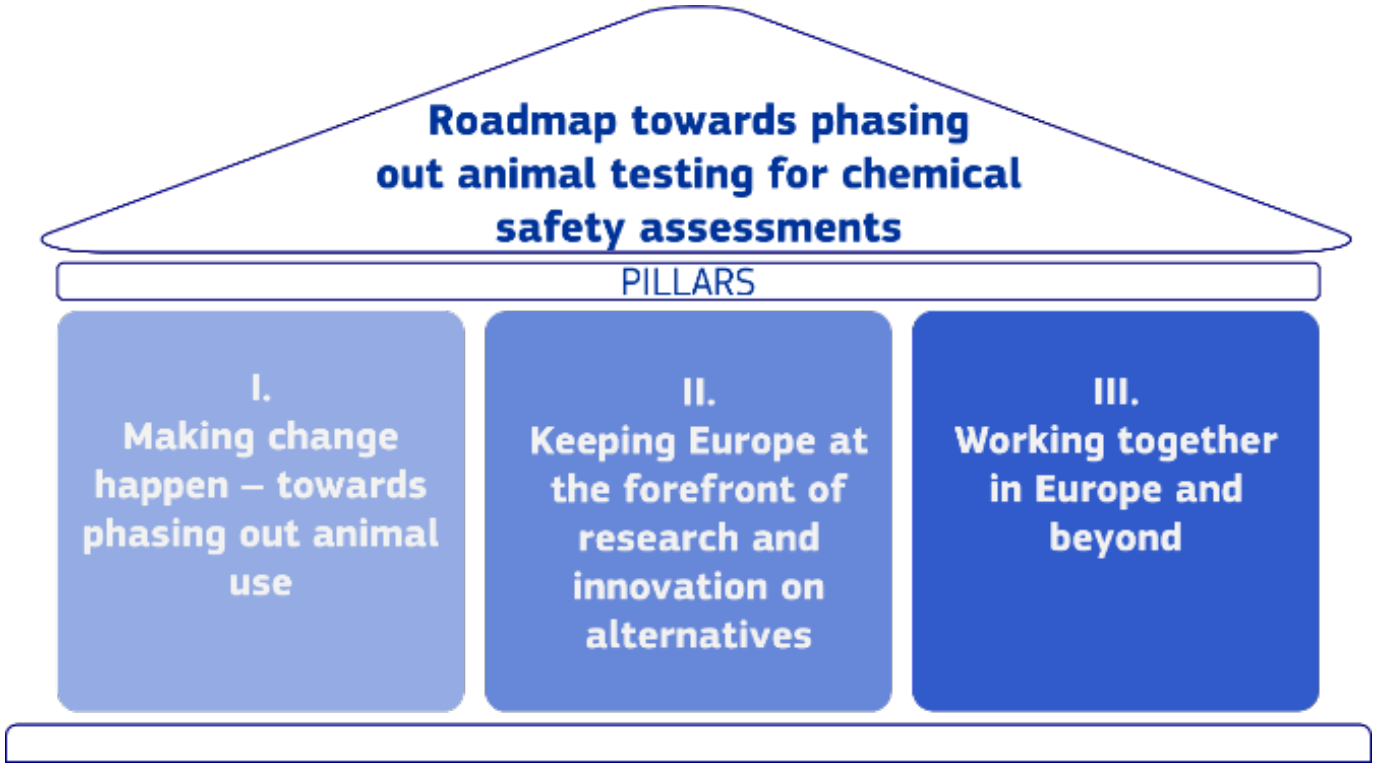
3



Cultural shift & Work as a community

Animal-free assessment is beyond simply replacing models shared commitment across the Pesticides community (and beyond)

WORK AS COMMUNITY



Roadmap has 22 policy actions

- **Several of them are a push to help us implementing**

  Eg.: Training, funding for research, development of information catalogues

- **Others cascade into actions by us**

  Eg.: Implementation of Staff Working recommendations; push for validation/qualification

STAFF WORKING DOCUMENT (SWD)

1. Developing a roadmap – a collective effort 7
1.1. Roadmap development through inter-service and inter-agency collaboration 7
1.2. Building a community through dedicated conferences and workshops 7
1.3. Listening to stakeholders – gathering evidence through consultations 7
1.4. Understanding change – stakeholder perspectives 8
2. Identifying opportunities towards phasing out animal use 9
2.1. Recommendation of actions for human health and environmental assessments 9
2.2. Preparing for the transition to animal-free chemical safety assessment 16
2.3. Overarching opportunities across Human Health and Environmental Safety 53
3. Recommendations and actions for environmental safety assessments 61
3.1. Acute fish toxicity 61
3.2. Aquatic and terrestrial bioaccumulation 65
3.3. Fish chronic toxicity 78
3.4. Endocrine disruption for environmental safety assessments 90
3.5. Birds and mammals 100
3.6. Ecological thresholds of toxicological concern and species sensitivity distributions 107
4. Recommendations and actions for human health assessments 109
4.1. Acute toxicity (human health assessment) 109
4.2. Genotoxicity 116
4.3. Carcinogenicity 125
4.4. Repeated dose toxicity 135
4.5. Developmental neurotoxicity - the DNT in vitro battery 163
4.6. Developmental and reproductive toxicity (DART) assessments 175
4.7. Endocrine Disrupting Chemicals - Use of New Approach Methodologies for their assessment within European Union regulatory frameworks: Recommendations from the 2024 EPAA Partners' Forum 186
5. Working together to design and implement non-animal approaches in regulatory testing 196
5.1. Role and composition of the roadmap steering team 196
5.2. Roadmap steering team 196
5.3. Engaging Member-State and stakeholder experts in agency collaborative structures 198
5.4. EU Agency Network (EUAN) – working group on animal-free approaches 199
5.5. Translating innovative methods into regulatory applications – validation, standardisation, qualification 201
5.6. Safe spaces and regulatory exploration spaces for animal-free methodologies 207
6. Indicators – managing change by measuring it 212

LINK

Areas covered in the scientific recommendations

- Next generation risk Assessment (NGRA)
- Acute fish tox
- long-term toxicity
- ADME
- Acute toxicity
- Omics
- Toxicokinetics (TK)
- Aquatic and terrestrial bioaccumulation
- Endocrine Disruption (ED)
- Reducing the number of animals & species
- Genotoxicity
- Carcinogenicity
- Developmental neurotoxicity (DNT)
- species sensitivity
- Nanomaterials
- Fish chronic toxicity
- Developmental & reproductive tox (DART)

(SUPPORT) DEVELOPMENT OF NAMs

NAMs Development

Some examples

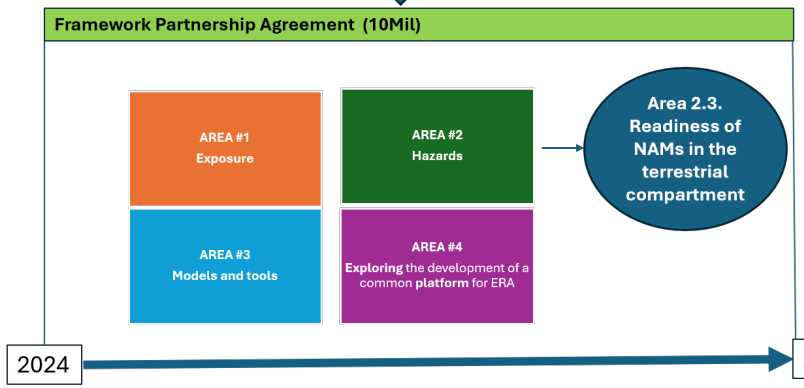


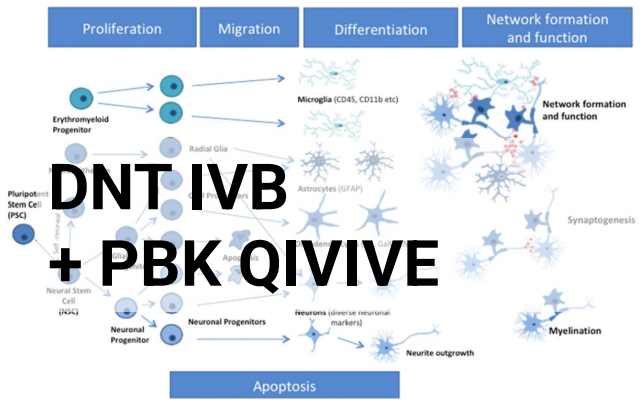


External scientific report | Open Access

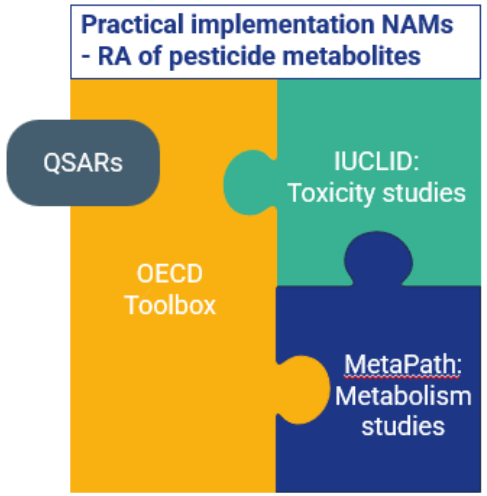
Development of an adverse outcome pathway network for reproductive toxicity endpoints to support identification of endocrine disrupters

ADVANCING THE ERA OF PLANT PROTECTION PRODUCTS TOWARDS A SYSTEM BASED APPROACH

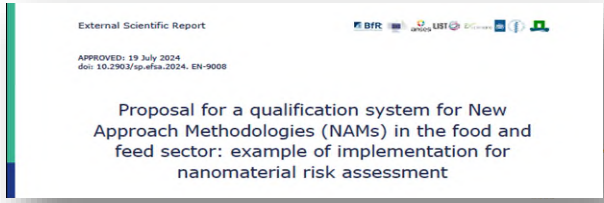




DNT IVB + PBK QIVIVE



EFSA NAMS4NANO PROJECT



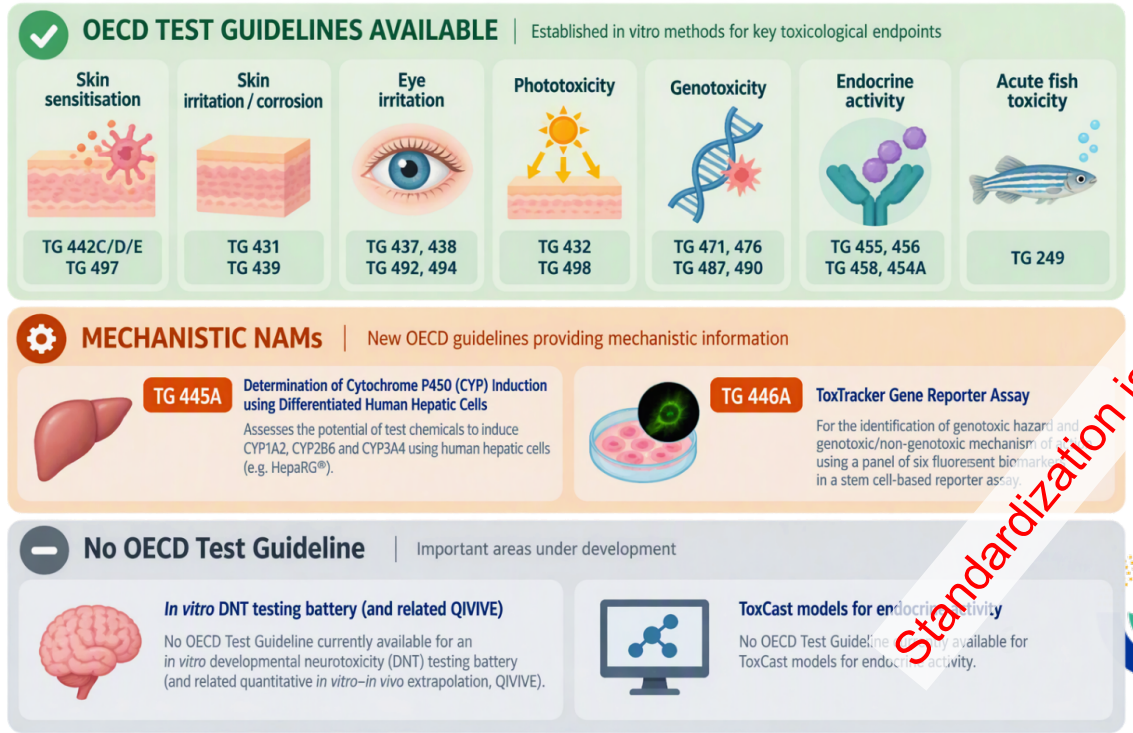
WHERE ARE NAMS BEING USED IN PESTICIDES?

OECD Test Guidelines:

- Skin sensitisation (TG 442C/D/E, TG 497)
- Skin irritation/corrosion (TG 431, TG 439)
- Eye irritation (TG 437, 438, 492, 494)
- Phototoxicity (TG 432, TG 498)
- Genotoxicity (TG 471, 476, 487, 490)
- Endocrine activity (TG 455, 456, 458, 454A)
- Acute fish toxicity (TG 249)
- Mechanistic NAMs:
  - TG 445A Determination of Cytochrome P450 (CYP) Induction using Differentiated Human Hepatic Cells
  - TG 446A ToxTracker Gene Reporter Assay for the Identification of Genotoxic Hazard and Genotoxic/Non-Genotoxic Mechanism of Action

No Test Guidelines:

- In vitro DNT testing battery (and related QIVIVE)
- ToxCast models for endocrine activity
- Endocrine MoA
- Supporting information and literature studies



THE REGULATORY IMPLEMENTATION IS PROBLEM-DRIVEN - NOT METHOD-DRIVEN

THE QUESTION IS NOT *"CAN A NAM REPLACE IN VIVO?"*

It is: how can NAM evidence contribute to answering a defined regulatory question?

Decision context

What decision is being supported?
What level of certainty is needed?

Biological relevance

Which mechanisms/key events are covered?
Where are important gaps?

Evidence integration

How do lines of evidence change the conclusion and its uncertainty?

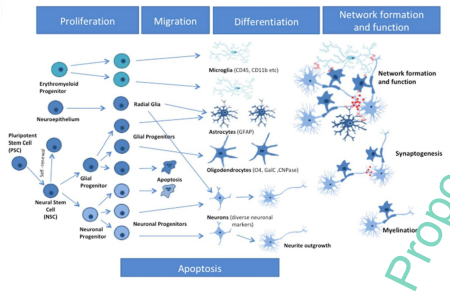
How can risk assessment profit from new technologies?
Can we re-think the assessment framework?

Science can drive Regulation

PESTICIDES DATA REQUIREMENTS – UNDER REVISION

Regulation (EU) No 283/2013 2026*

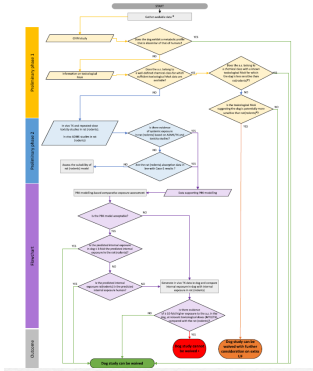
Available methodologies for conducting regulatory studies and risk assessments have evolved. In particular, ***new approaches for conducting risk assessments and new study protocols that may include alternatives to animal testing*** *have become available while certain others have become obsolete.*

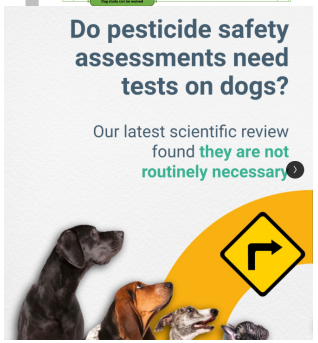


Proposed

Instead of supplementary in vivo DNT based on triggers:

- Including the **assessment of all pesticide active substances for DNT**,
- Requires adaptations of the existing regulatory framework.
- Considers the implementation of the DNT IVB and IATA





5.3.2. Oral 90-day study

→ A study in dogs shall be reported **unless** it is *scientifically justified to not submit such study*.

▼

Before undertaking in vivo studies, a
An analysis shall be performed adopting a tiered approach.
The testing strategy shall take into account validated non-animal approaches and testing e.g. bridging or read-across principles, in silico studies, in vitro study protocols.

CURRENT LEGAL AND SCIENTIFIC CONSIDERATIONS

Regulation (EU) No 283/2013

- In general, for pesticides substances the dossier shall include studies **fulfilling the data requirements under Regulation (EU) No 283/2013.**

Nonetheless,

- well-supported waivers and non-testing approaches (including modelling), are already regularly accepted **case by case**, particularly where:
  - information is not necessary due to the nature of the substance/uses
  - According to Reg. 1107/2009 Article 62(1) first sentence "*Testing on vertebrate animals for the purposes of this Regulation shall be undertaken only where no other methods are available.*"

THYROID WORKSHOP BY EFSA/ECHA/JRC

Workshop on Species Differences in Liver-mediated Thyroid Disruption: Scientific and Regulatory Considerations

Date: 11-12 May 2027
Location: Brussels

Information on expression of interest soon

Main aim(s):

- Investigate harmonise of scientific and regulatory approaches for assessing species differences in liver-mediated thyroid mode of action (MoA).
- Evaluate the status and performance of *in vitro* methods for hepatic enzyme induction (especially Phase II).
- Develop scientific criteria for determining when such methods are reliable and regulatory relevant.
- Explore how these methods can support weight-of-evidence for endocrine disruptive properties.

All outcomes will be included as (non-binding) recommendations in a workshop report

Participants:

Participants need to be active actors with knowledge in the field (Thyroid disruptions with liver MoE and/or in vitro method validation)

- Identified experts will be invited
- Registration will be open for expression of interest - but subjected to EFSA/ECHA/JRC approval
- Balanced stakeholder representation will be sought

Format:

- Background information will be provided
- Participants with Key knowledge/scientific updates on the topic (both biological and methodological) will be invited to present
- Agencies will share some case studies in the plenary meetings
- Break-out groups will be organised for discussion and agreement on specific technical aspects

Standardization is needed!

VALIDATION VS QUALIFICATION

OECD Test Guidelines

- ✓ **Standard methods** for safety testing of chemicals
- ✓ **International use**
- ✓ **Internationally agreed regulatory readiness**



✓ **Mutual Acceptance of Data** (MAD)

Validation

- ✓ **Validation studies** based on internationally recognised principles (OECD GD 34)
- ✓ **Validation bodies** or other actors (e.g. method developers, public-public or public-private partnerships)

Pepper

EURL ECVAM — European Union Reference Laboratory for Alternatives to Animal Testing

JaCVAM

UNITED STATES ICCVAM — Advancing Alternatives to Animal Testing

Qualification Opinion

- ✓ **Expert opinion** based on pre-defined criteria
- ✓ **EFSA context-specific regulatory readiness**



✓ **Context of use** (e.g, one legal framework)

Qualification

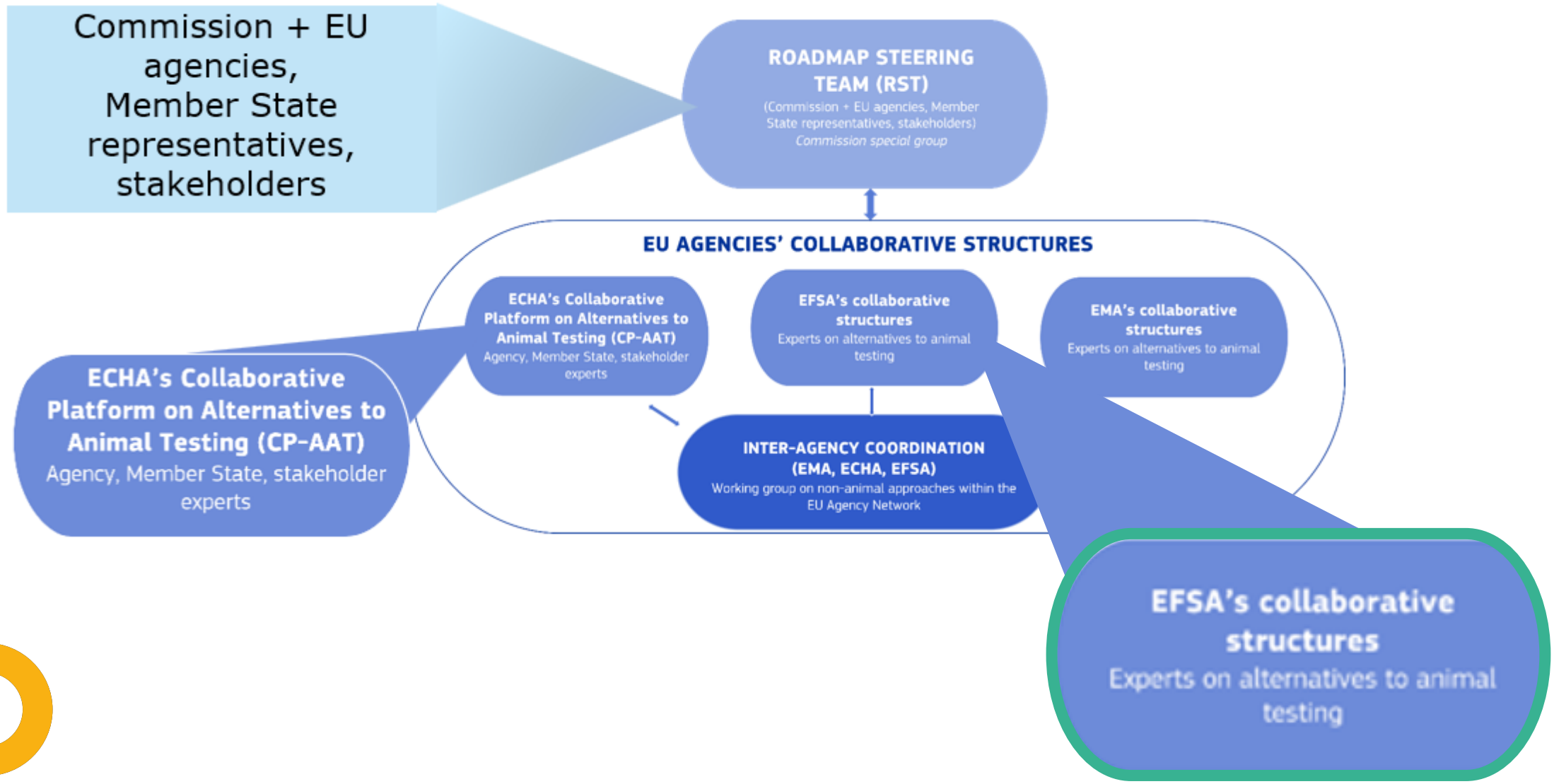
efsa NAMs NANO

Proposal for a qualification system for NAMs for nanoparticles risk assessment in the food and feed chain

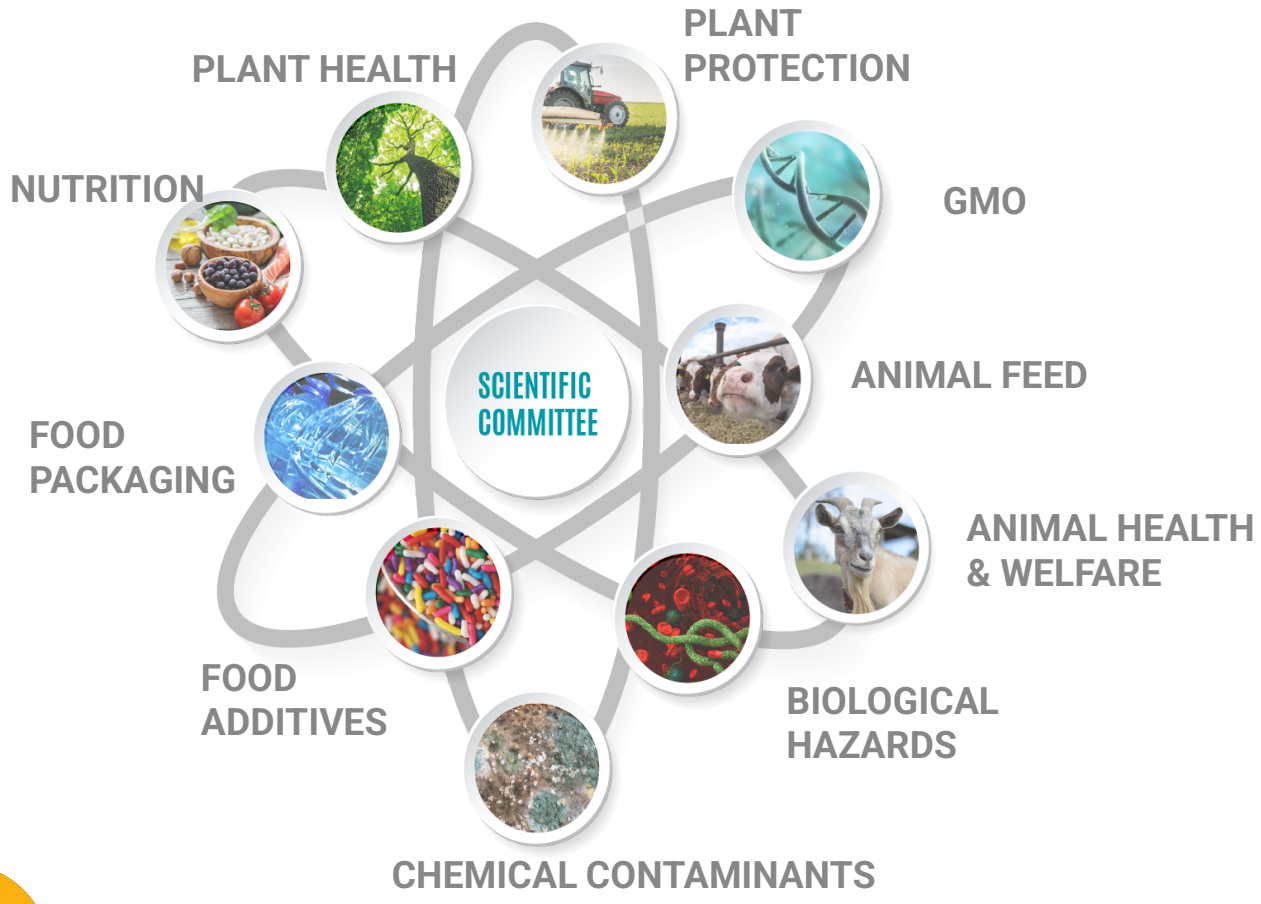
- ✓ **Voluntary,** practical tools **aiming toward faster regulatory implementation** of non-guideline methods

✓	**Test method definition/description** ✓
✓	**Relevance** ✓
✓	**Within-lab reproducibility** ✓
✓	**Between-lab reproducibility** — *Optional, but must demonstrate transferability to at least one lab*

GOVERNANCE MODEL FOR THE IMPLEMENTATION OF ROADMAP

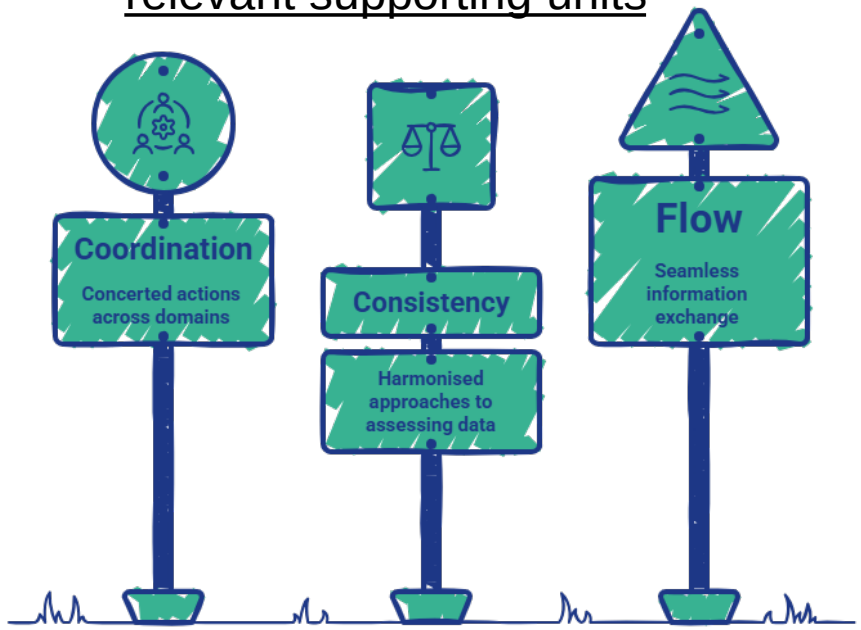


EFSA´S REMIT & LEGAL FRAMEWORK



EFSA Advisory Group on Integration of NAMs in EFSA risk assessment

EFSA staff from all scientific units, panels and relevant supporting units



Data Requirements

EFSA Guidance

NEW ADME/PBK WG & Guidance

AI for science (AI4SCI) Fusion Team

STRONGER TOGETHER TO IMPLEMENT NAMS

EU MS Food Safety Agencies

European Commission

PARC

食品安全委員会
Food Safety Commission of Japan
内閣府
Cabinet Office

Global Coalition for Regulatory Science Research

EFSA SC & Panels

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

epaa
The European Partnership for Alternative Approaches to Animal Testing

World Health Organization

efsa
EUROPEAN FOOD SAFETY AUTHORITY

ECHA
EUROPEAN CHEMICALS AGENCY

FDA

ASPIS

EUTOXRISK

OECD
BETTER POLICIES FOR BETTER LIVES

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

CFSA 国家食品安全风险评估中心
China National Center for Food Safety Risk Assessment

ILMERAC

APCRA
ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT

STAY CONNECTED

SUBSCRIBE TO
efsa.europa.eu/en/news/newsletters
efsa.europa.eu/en/rss
Careers.efsa.europa.eu – job alerts

LISTEN TO OUR PODCAST
Science on the Menu –Spotify, Apple Podcast and YouTube

FOLLOW US ON BLUESKY
@efsa.bsky.social
@efsa-animals.bsky.social @efsa-plants.bsky.social

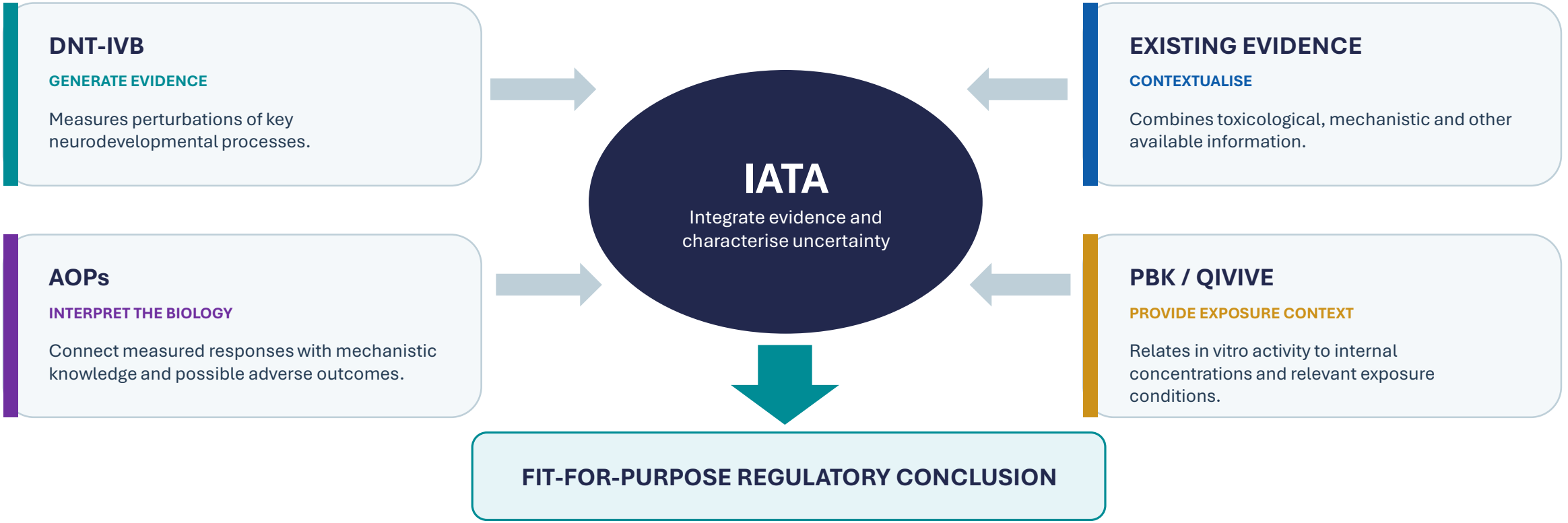
FOLLOW US ON LINKEDIN
Linkedin.com/company/efsa

FOLLOW US ON INSTAGRAM
@one_healthenv_eu

CONTACT US
efsa.europa.eu/en/contact/askefsa

EUROPEAN FOOD SAFETY AUTHORITY

BUILDING A FRAMEWORK FOR REGULATORY USE: THE BUILDING BLOCKS



Regulatory confidence develops through repeated application of this framework to real assessment questions.

What Have We Learned from DNT IVB IATA Regulatory Case Studies?

1	**START WITH THE REGULATORY QUESTION**	The context of use determines the evidence required and the acceptable level of uncertainty.
2	**EVALUATE THE EVIDENCE SYSTEMATICALLY**	Reliability, biological relevance, applicability and data quality must be assessed transparently.
3	**INTEGRATE, RATHER THAN REPLACE**	DNT-IVB data contribute alongside toxicological, mechanistic, kinetic and exposure evidence.
4	**CHARACTERISE UNCERTAINTY EXPLICITLY**	Assumptions, limitations, evidence gaps and their impact on the conclusion must remain visible.
5	**LEARN THROUGH APPLICATION**	Regulatory case studies generate experience to define criteria for use and develop a standard decision framework.

Regulatory case studies transform a promising battery into decision-relevant regulatory evidence.