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# AI-augmented NGRA: Opportunities to Accelerate Phase out of Animal Testing for Chemical Safety Assessment

SERS
Safety, Environmental & Regulatory Science




Predrag Kukic

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# EU Roadmap to Phase out Animal Testing: Cross Sector Animal Free NGRA

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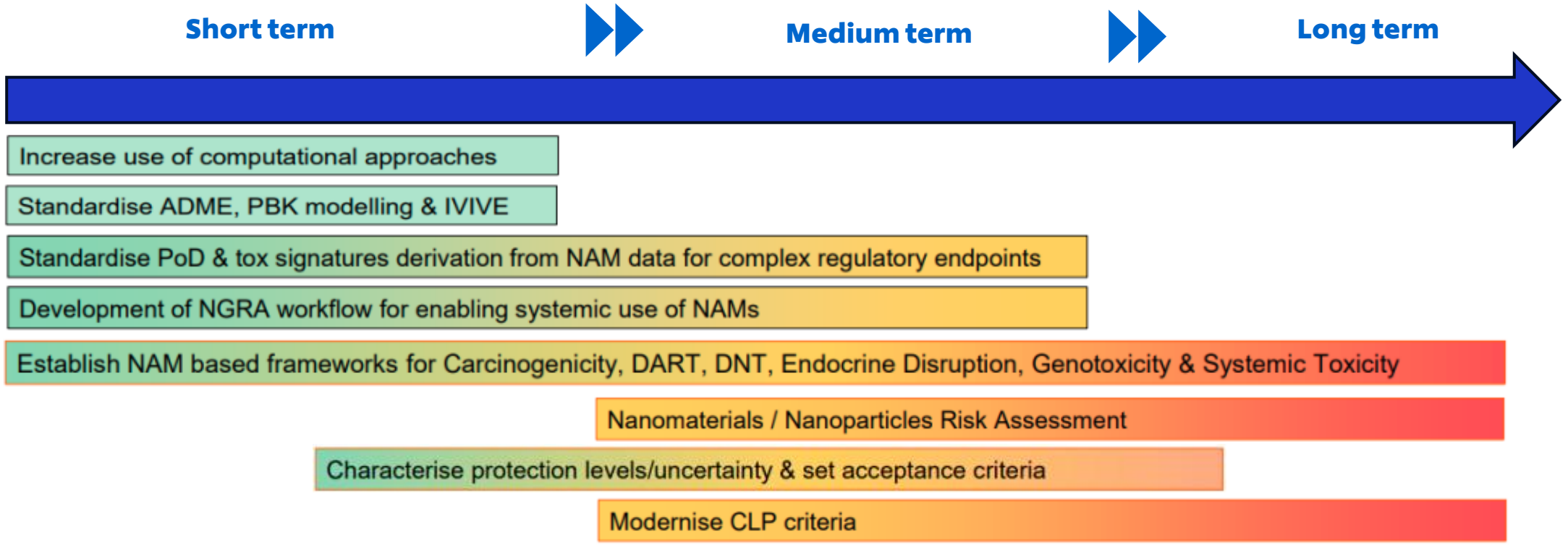

# EU Roadmap to Phase out Animal Testing: Cross Sector Animal Free NGRA

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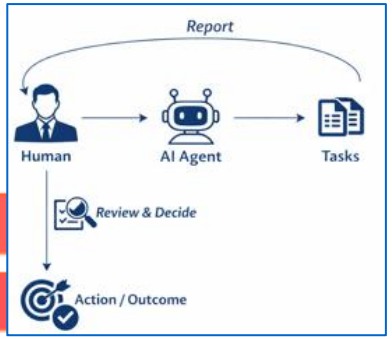
**Short term** → **Medium term** → **Long term**

- Increase use of computational approaches
- Standardise ADME, PBK modelling & IVIVE
- Standardise PoD & tox signatures derivation from NAM data for complex regulatory endpoints
- Development of NGRA workflow for enabling systemic use of NAMs
- Establish NAM based frameworks for Carcinogenicity, DART, DNT, Endocrine Disruption, Genotoxicity & Systemic Toxicity
- Nanomaterials / Nanoparticles Risk Assessment
- Characterise protection levels/uncertainty & set acceptance criteria
- Modernise CLP criteria



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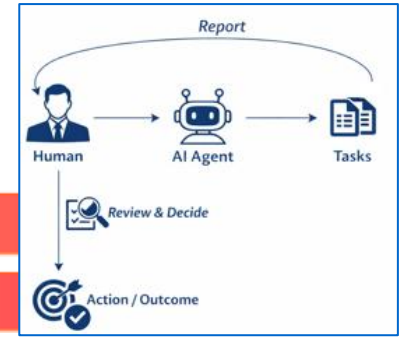


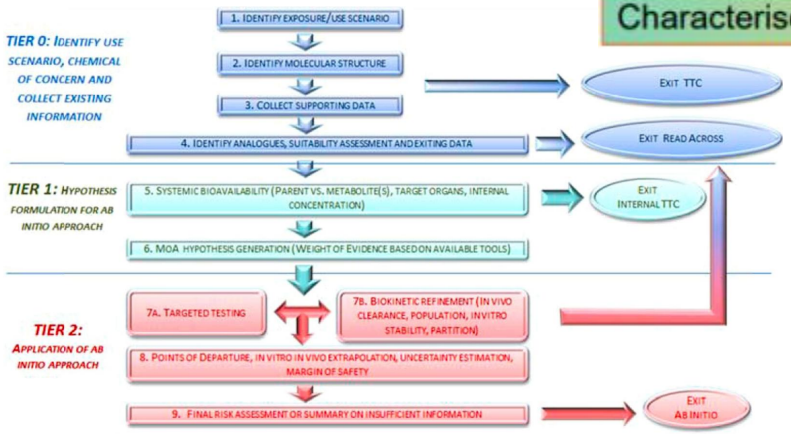


*Berggren et al, 2017*

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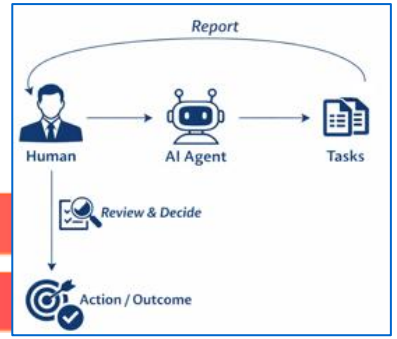


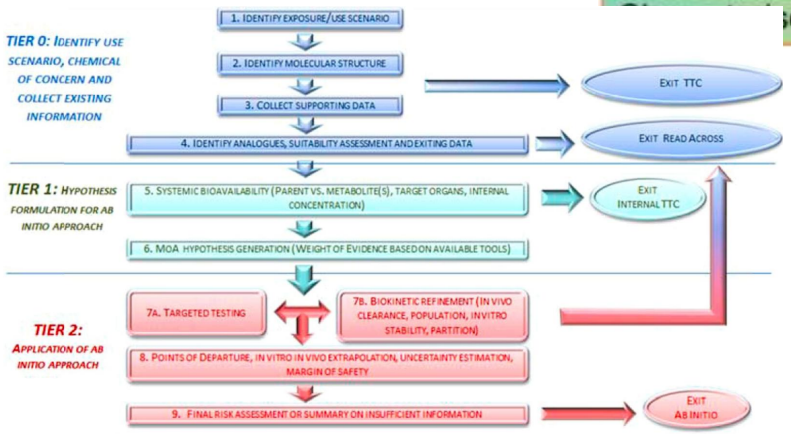


*Berggren et al, 2017*

# AI Augmented NGRA: AI is transforming NGRA across 3 dimensions

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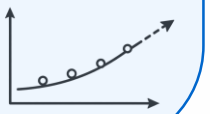
## Knowledge/Data

- Extract insights from diverse data sources
- Enable mechanistic interpretation
- Support hypothesis generation

## Prediction/Decision

- Generate predictions from data
- Model hazard and exposure
- Quantify risk and uncertainty



## Standardisation/ Automation

- Automate existing workflows
- Reduce routine manual effort

Development of NGRA workflow for enabling systemic use of NAMs

Standardise PoD & tox signatures derivation from NAM data for complex regulatory endpoints

Characterise protection levels/uncertainty & set acceptance criteria

Modernise CLP criteria

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Standardise ADME, PBK modelling & IVIVE

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# Knowledge/Data: Extract Insights from Diverse Data Sources

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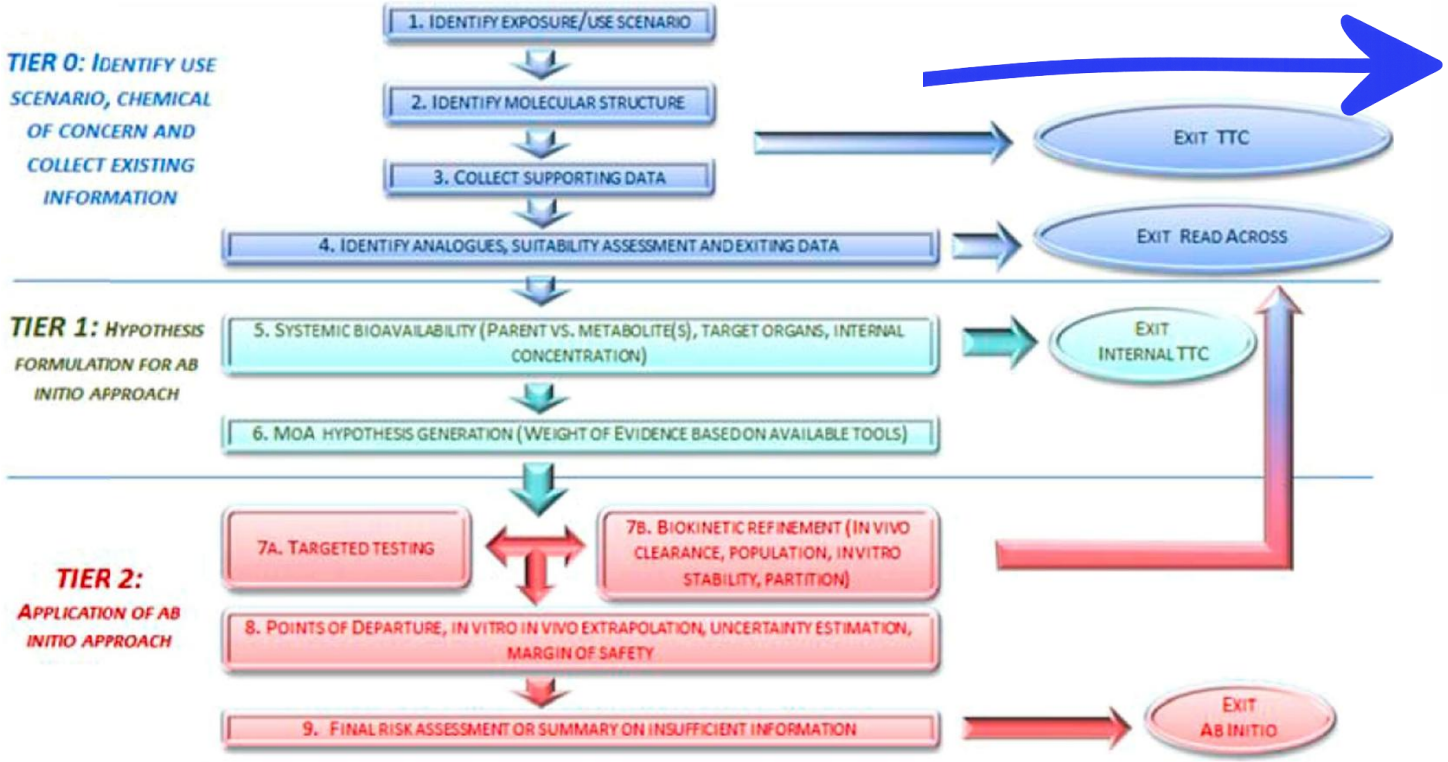


*Berggren et al, 2017*

## Integration of structured and unstructured data


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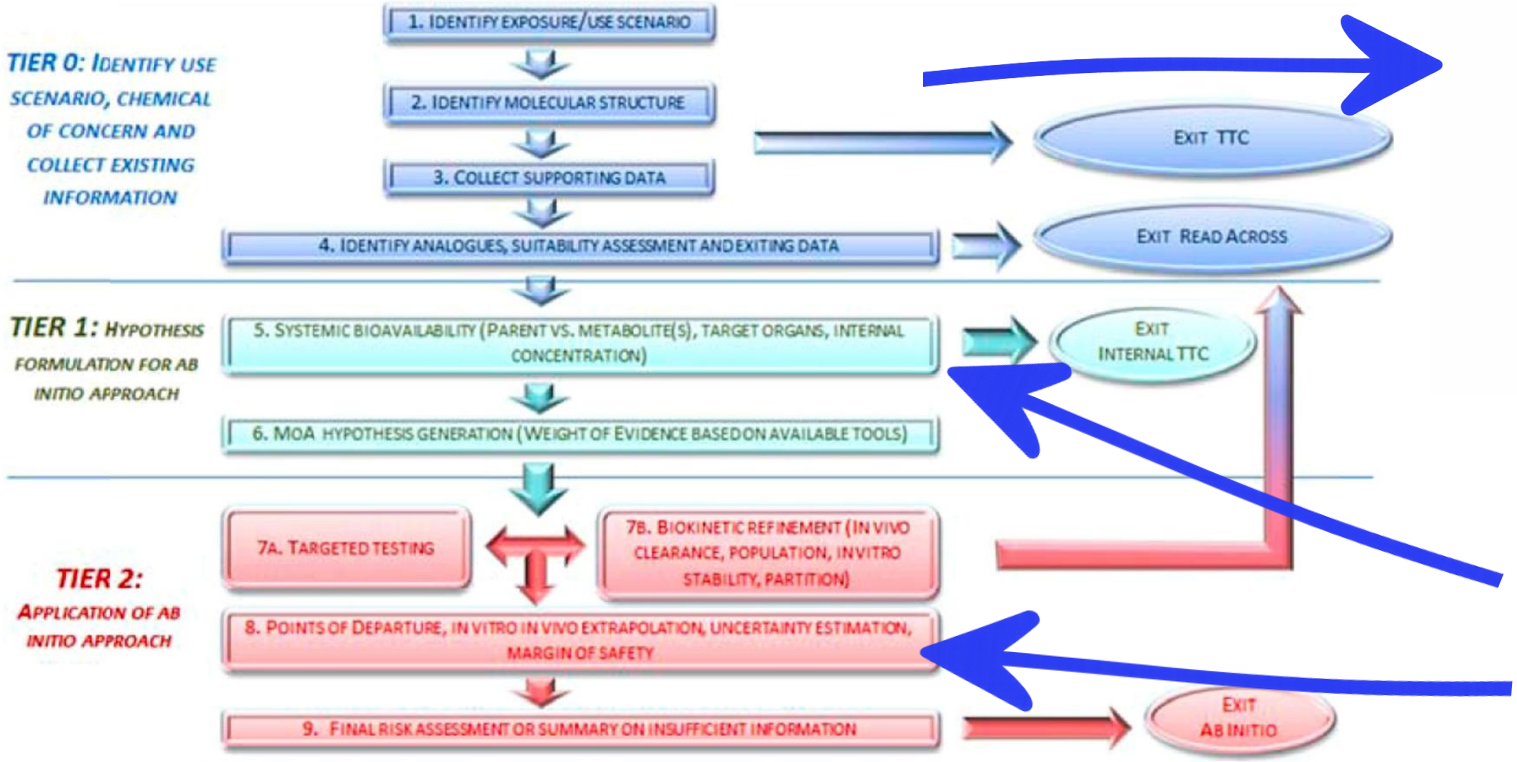
Standardise PoD & tox signatures derivation from NAM data for complex regulatory endpoints

Characterise protection levels/uncertainty & set acceptance criteria

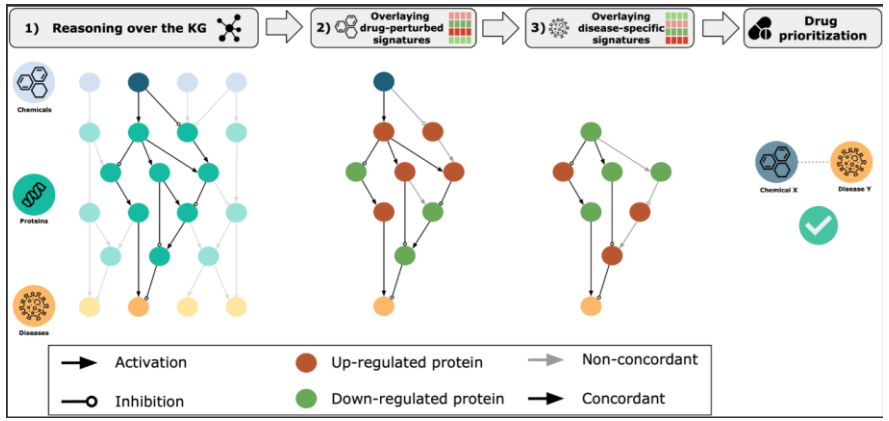
# Knowledge/Data: Support Hypothesis Generation and Mechanistic Interpretation




*Berggren et al, 2017*

## Integration of structured and unstructured data


**Example**: *Causal reasoning & hypothesis generation*




*Domingo-Fernández et al, 2022*

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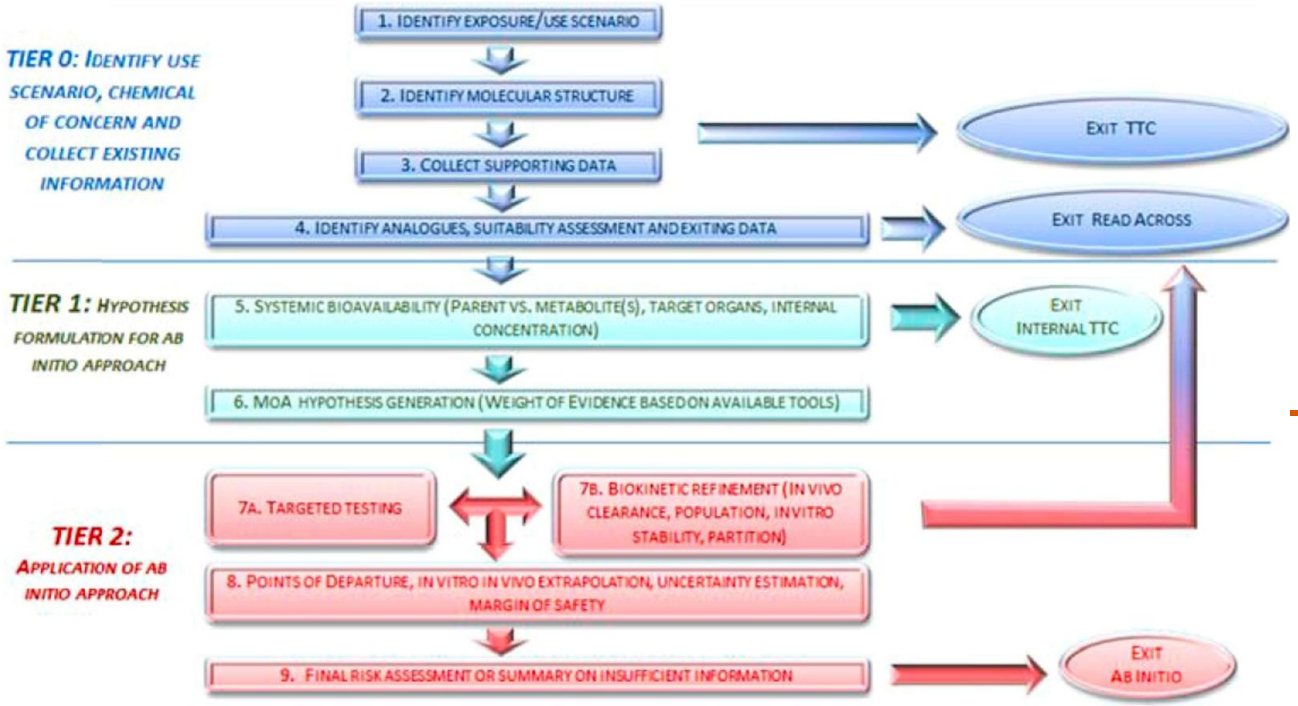
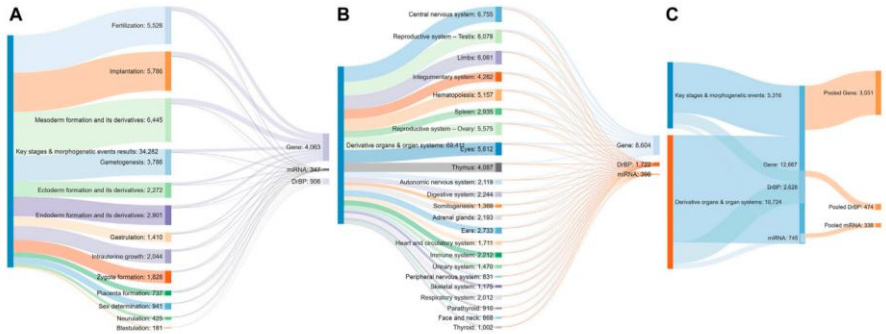
# Knowledge/Data: Biological Relevance of the NGRA workflow



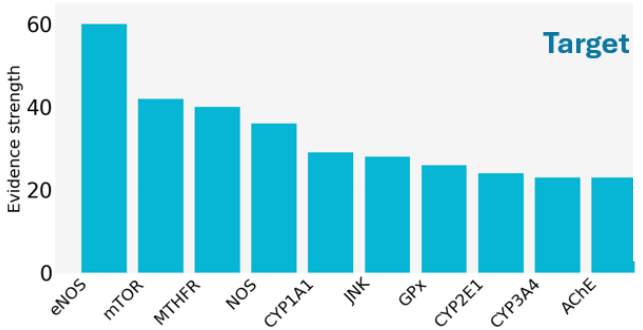

*Berggren et al, 2017*

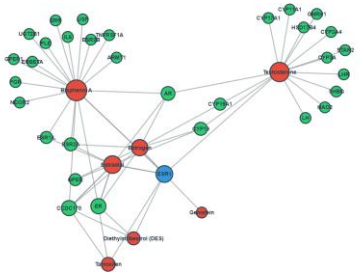
## Extraction of essential genes for Human Development and Reproduction




*Rajagopal et al.,(2022)*

## Defining Biological Space coverage in Systemic Toxicity Molecular and cellular targets



*Shobair et al, in progress (ICCS)*

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# Predictions/Decisions: Quantification of Biological Similarity at Scale/Read-Across

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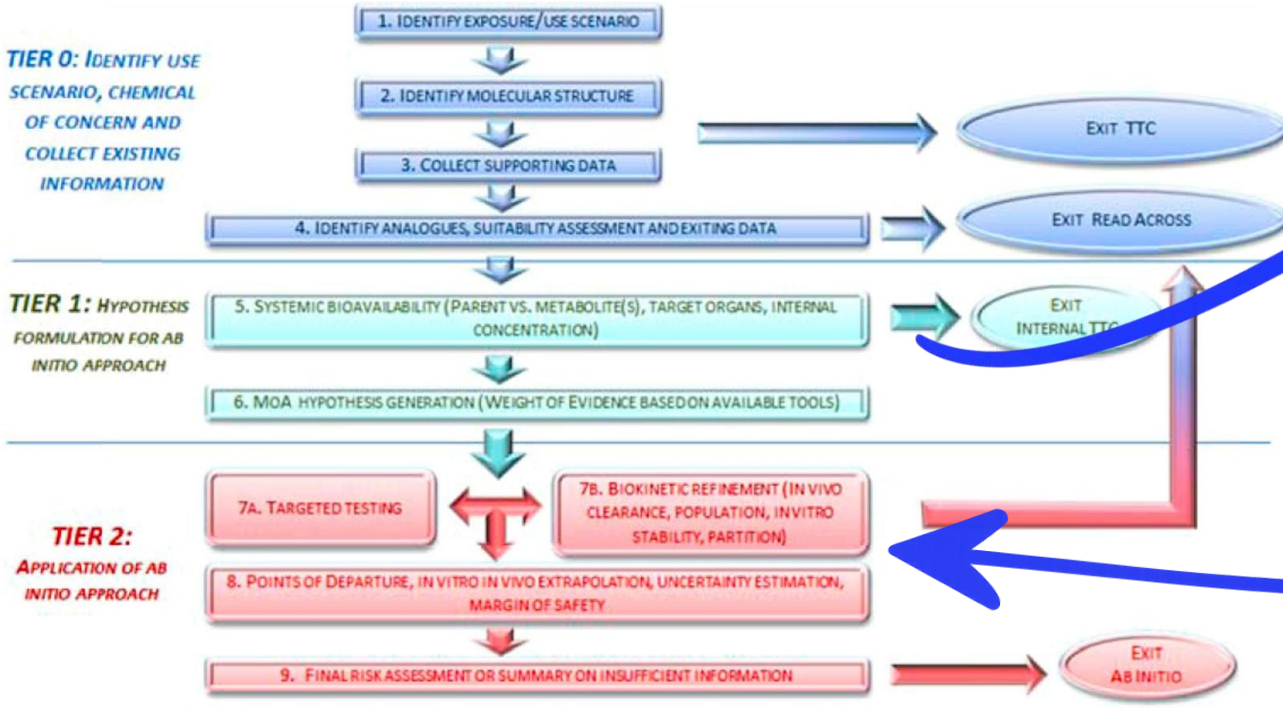
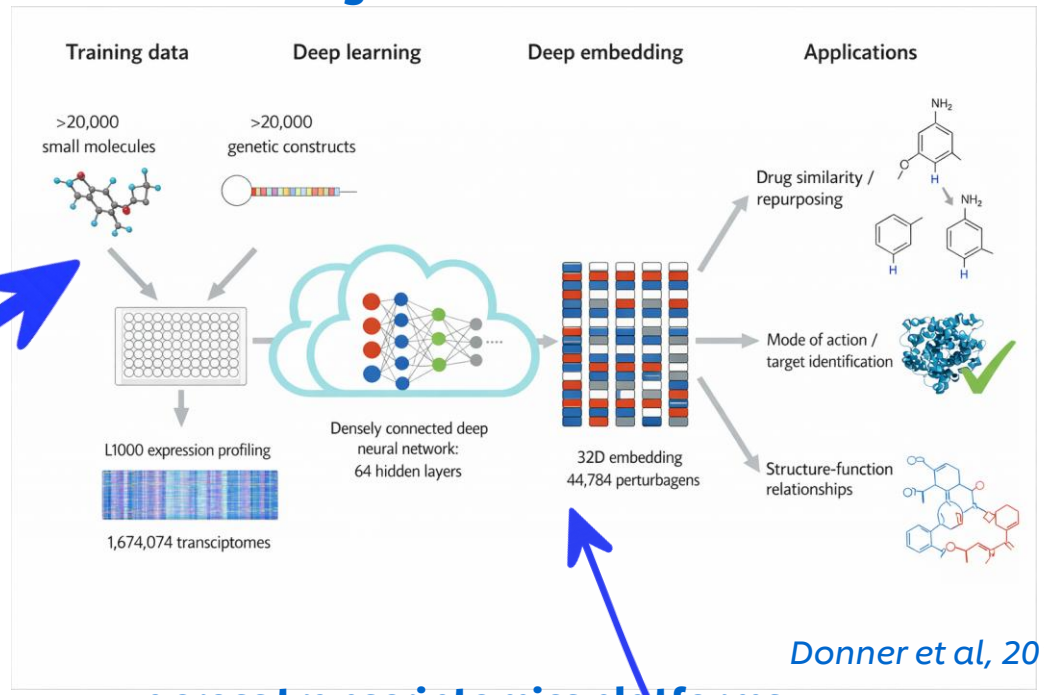


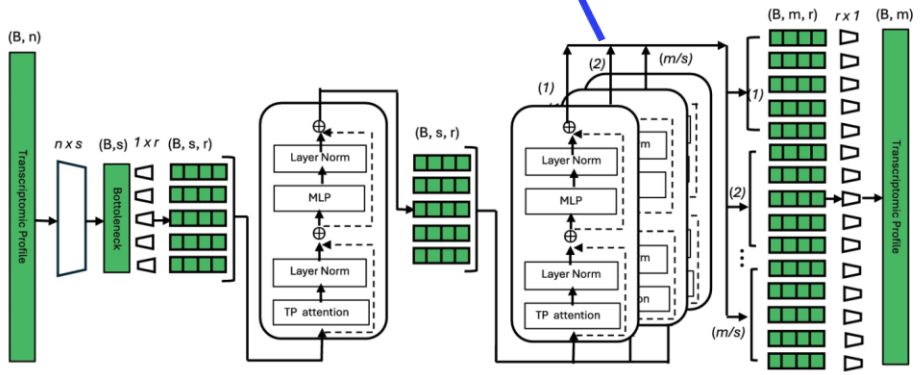

*Berggren et al, 2017*

## Metric learning …




*Donner et al, 2018*

## … across transcriptomics platforms




*Cong et al, 2026*

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# Standardisation/Automation: Agentic Workflows

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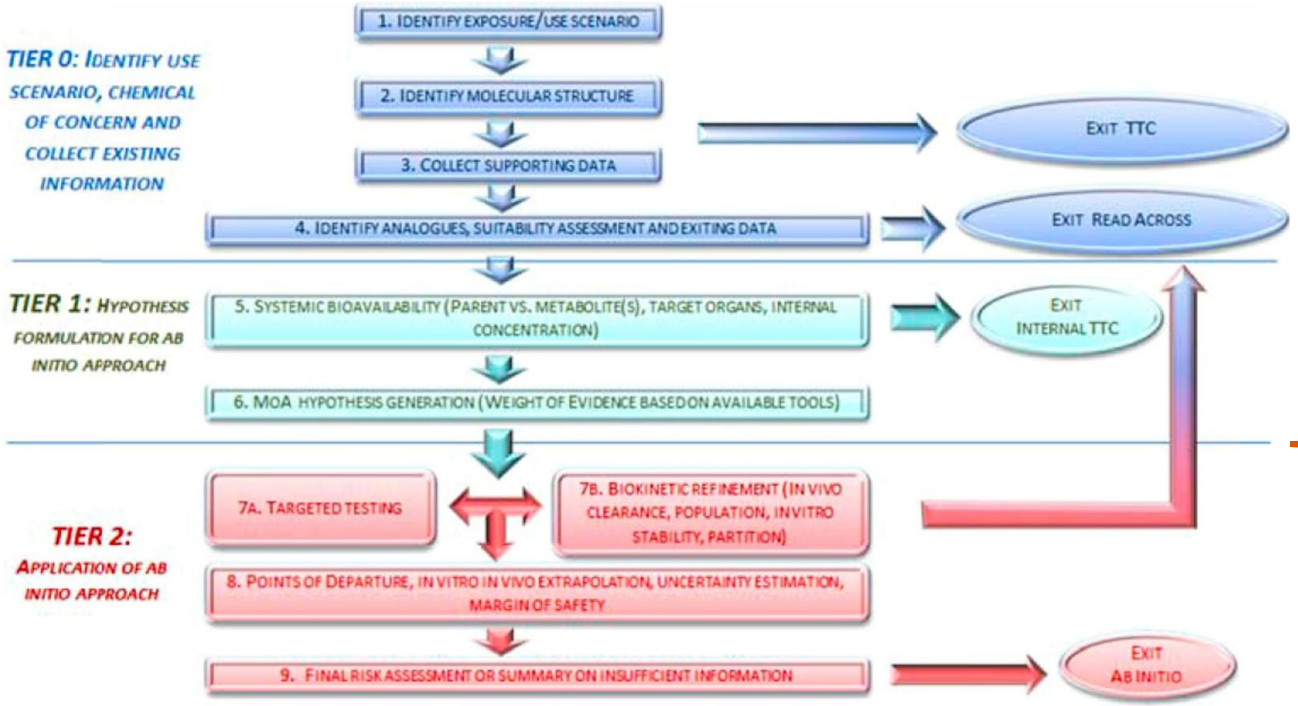
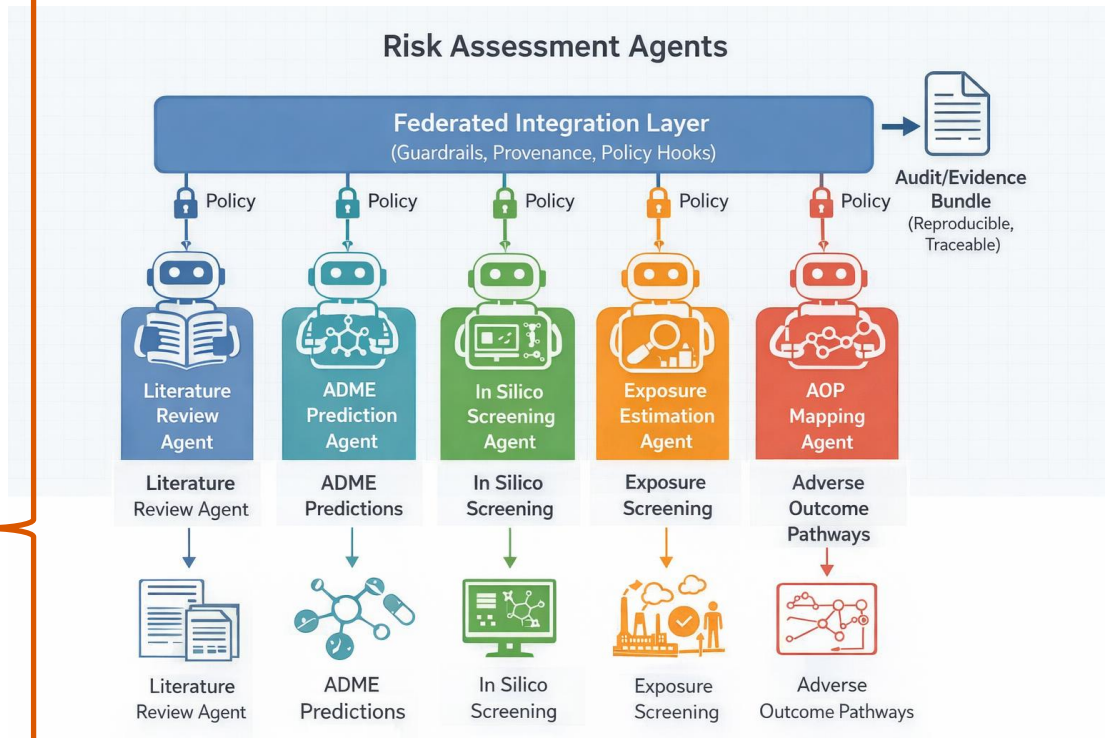



*Berggren et al, 2017*

## Automation of Tier 0 and Tier 1 workflows




*Based on ToxMCP, Djidrovski, 2026*

- Consistency and tractability of outcomes & decisions
- Enables application where specialised expertise was a barrier
- Increased productivity
- Holistic integration across expertise teams

Standardise ADME, PBK modelling & IVIVE

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# Building confidence in AI-augmented NGRA workflows: Responsible adoption

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### Proportionate Governance

Adoption of AI requires proportional validation and governance based on clearly defined use case and potential scientific and regulatory impact.

### Transparency and Traceability

AI-supported outputs should remain traceable to underlying evidence.

### Reproducibility and Change control

AI outputs should remain governable over time and variability should be monitored and controlled.

### Human Accountability

AI should assist decisions with human oversight, clear responsibilities, and communication of uncertainty.

### Data Governance and IP

AI use must comply with expectations relating to confidential information, data governance, secure handling of data, IP, licensing and liability.

Use **case studies** to build shared understanding and **practical guidance** on how to evaluate AI-augmented frameworks.

| Failure Class | Description | Critical Impact |
|---|---|---|
| **Epistemic Hallucination** | Fabrication of plausible but factually incorrect content | Erroneous medical or military decisions based on false information |
| **Overconfidence Failure** | High-confidence presentation of incorrect outputs | Human operators accept errors without scrutiny |
| **Abstention Failure** | Inappropriate refusal to respond when a response is needed | System paralysis at critical decision points |
| **Prompt Fragility** | Output instability across semantically equivalent phrasings | Unpredictable system behavior in diverse operational conditions |
| **Temporal Drift** | Performance changes across model versions and time | Undetected reliability regression following post-deployment updates |
| **Reasoning Collapse** | Incoherence, repetition, or truncation under complex reasoning demands | Failure during time-critical operational tasks |
| **Agentic Escalation** | Autonomous execution of unsafe or unintended actions | Irreversible operational or physical consequences |
| **Adversarial Manipulation** | Prompt injection causing deviation from intended instructions | Command hijacking by deliberate adversaries |

*Vadlapati et al, 2026*

# AI-augmented NGRA opportunities to Accelerate Phase out of Animal Testing for CSA: Areas where multi collaboration between regulators, industry and academia can help

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## Increased access to toxicological data that are FAIR

- Clear strategy on **shared infrastructure** - avoid fragmentation and siloing and work toward a unified machine-readable repository of legacy and NAM data (e.g. EBI/EMBL databases, ICE NTP curated database)
- Harmonise **data standards** - strengthen quality of data generation, transferring and processing (e.g. GIVIMP OECD 2018, standardized QC criteria), interoperability (e.g. OECD omics reporting templates)
- Coordinate efforts in high quality **NAM data generation** for large numbers of chemicals (e.g. OpenBind public/private consortia that powers next generation AI-based drug design, ToxCast/Tox21) and encourage pre-competitive data sharing

## Collaborative validation, shared understanding and joint-confidence building

- Adopt **next generation validation** frameworks that go beyond performance metrics and include important governance principles
- Bridge the research-to-regulatory-use gaps for AI-augmented workflows e.g. commission **multi-stakeholder pilot projects for early, open and constructive engagement** and case studies to build confidence in priority areas
- Utilise **sandbox environments** where industry can test AI tools against clearly defined regulatory expectations

## Facilitate training and capacity building on AI literacy for safety scientist, data scientists and regulators

# Acknowledgements

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40+ years of developing non-animal safety science

70+ collaborations

600+ publications

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