

NGRA / DATA FRAMEWORK
Information need → Evidence generation → Decision

Stage 1
Hazard Landscape Construction



- QSAR / HTS
- Structural alerts
- Endpoint prioritization
- MIE clues

Stage 2
Exposure Route Decision Hub



- Dermal penetration
- Metabolism prediction
- POPK estimation
- Route reconstruction
- Exposure route = decision variable

Stage 3
MIE-driven Mechanism Assessment



- MIE status-based mode selection
- AOP-informed analysis
- Mechanistic evidences

Stage 4
Confidence-weighted Weight Integration / IATA Decision



- Evidence weighting
- Conflict resolution
- IATA-guided decision
- Uncertainty handling

Clear Positive



Consistent high-confidence evidence of adverse potential

Positive with Concerns

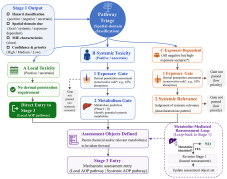


Evidence gap or uncertainty; targeted testing recommended

Credible Negative



Consistent low-risk conclusion with adequate evidence



MIE status / knowledge

Mode 1

MIE known and predictable



Function

Predict and attribute MIE occurrence

Approach

Targeted models, mechanistic simulations, molecular docking

Output

Direct mechanistic evidence anchored to MIE

Mode 2

Pre-MIE-to-MIE hierarchy within AOP



Function

Sequential screening along pre-MIE hierarchy

Approach

Tuned in silico models, QSAR, cheminformatics, pathway mapping

Output

Partial AOP pathway evidence

Mode 3

MIE undefined or not formalized



Function

Statistical association and network inference

Approach

Network inference, pathway enrichment, molecular docking

Output

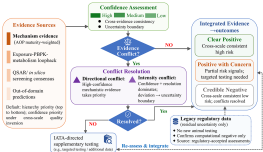
Supportive evidence (lower mechanistic specificity)

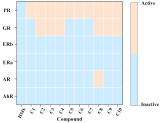
AOP maturity modulation (does not alter mode assignment)

AOP quantitative $\rightarrow$ MIE attribution extends downstream along KE chain

AOP qualitative/putative $\rightarrow$ Actionable range restricted, evidence weight downgraded and flagged for Stage 4 Well-weighting









HMS Case Study: Representative endpoint pathways



Screen



Route



Mechanism



ToE & LCA

ERα Agonism (endocrine activity)

Key evidence



In silico screening
ToxTEXT + EDC Profiler
→ ERα positive



Metabolic trend
Consistent with QSAR trend



Molecular docking
Supports ERα binding



Clear Positive
(High confidence)

Skin Sensitization (immune-mediated)

Conflicting computational evidence

Toxicer

Negative
(High confidence)

VS

VEGA QSAR

Positive
(Medium-low confidence)

ToE resolution



High confidence
mechanistic
evidence prioritized



SOP legacy data
confirms credible
negative



Credible Negative
(Medium-high confidence)

Metabolic PR Shift (metabolite-mediated activity)

Metabolic transformation

Parent HMS

PR
inactive



10 metabolites
PR active



Docking
Supports
PR binding



Positive With Concerns
(Medium confidence)



LATA: targeted PR validation

1

Screen



Hazard Screening

2

Exposure & Route



Dermal

3

Mechanism



MIE → ACP

4

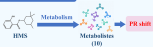
WoE & LATA



Evidence Integration

Metabolite-driven refinement

HMS case study



Key outcomes



ERa

Clear Positive



Skin Sensitization

Credible Negative



PR metabolites

Positive with Concern