ASPIS

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ONTOX

PRECISION TOX

RISK HUNT3R

OECD IATA and ASPA Case Studies: lessons and take home messages

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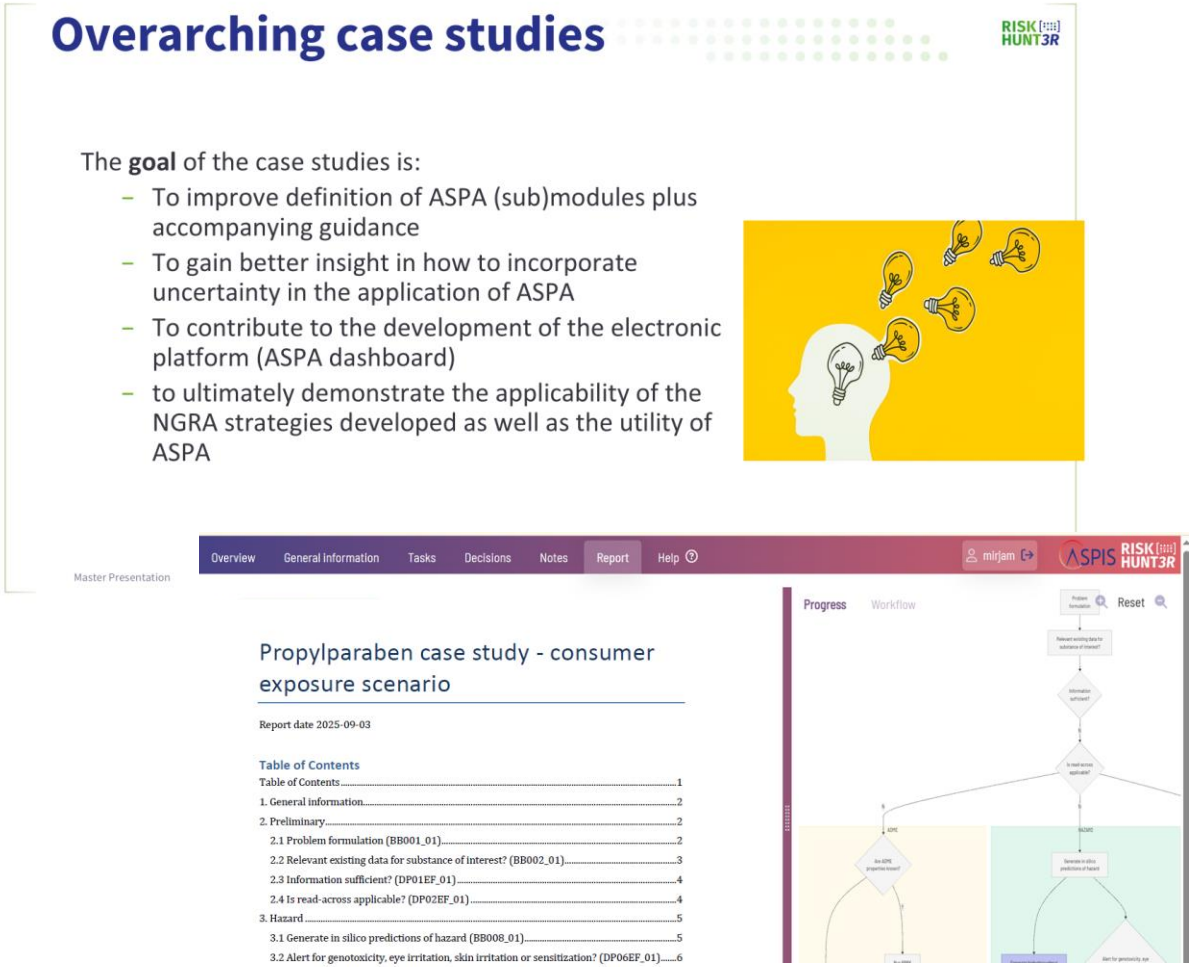
Background

- The OECD IATA Case Studies Project allows countries to share and explore the use of novel methodologies in IATA for evaluating the safety of chemicals within a regulatory context.
- Within each submission cycle for each approved case studies are published with a consideration documents capture learnings and lessons from the review experience.
- These submissions are time consuming and resource intensive both from the side of the submitters and also the reviewers
- During 2025 5 case studies were submitted – 3 of these were from RiskHunt3r

Case studies –build confidence

- Build out from specific independent examples rather than discussing hypotheticals
- Range of stakeholders around the table to get different technical capabilities – method developers, industry and regulators
- Focus on the information and solutions that are being developed in relation to the decision needs
- Demostrate applicability and utility while also demonstrating gaps in current status
- Enables iteration and improvement



Feedback from OECD meeting

- Overall experience was very positive
- Gained first-hand experience of how outputs from the projects can directly drives real-world impact
- IATA emphasizes transparent, accountable reporting of all results

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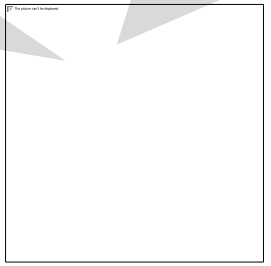
CS 2025-03,4, 5

- ASPA workflow
- OPERA QSAR tool
- VEGA prediction for an inconclusive or out of applicability domain prediction.
- ADME tool
- Chemical Effect Predictor
- Simulation of internal concentrations using Simcyp (webinar)
- TXG-MAPr (webinar)
- KNIME workflow for deriving the model, data transformation and machine learning.

- How to incorporate aggregate exposure estimates and PBK modeling to translate external doses into internal concentrations and apply BER concept
- Which endpoints or responses were examined to assess systemic toxicity
- How to Choose ASPA modules and assess their applicability based on problem formulation assumptions.

"... in a guidance it should be explained how studies should be conducted" "...The biggest problem is how to standardize the tools that generate information sources. Without a set standard, differences will arise between evaluators, leading to variations in the certainty of the results."

" It would assist to have clarification as when to progress to next module or when a person should stop due to being not appropriate or necessary to progress to next module. For example, is there a minimum number of 'positive' bioactivity assays needed to progress



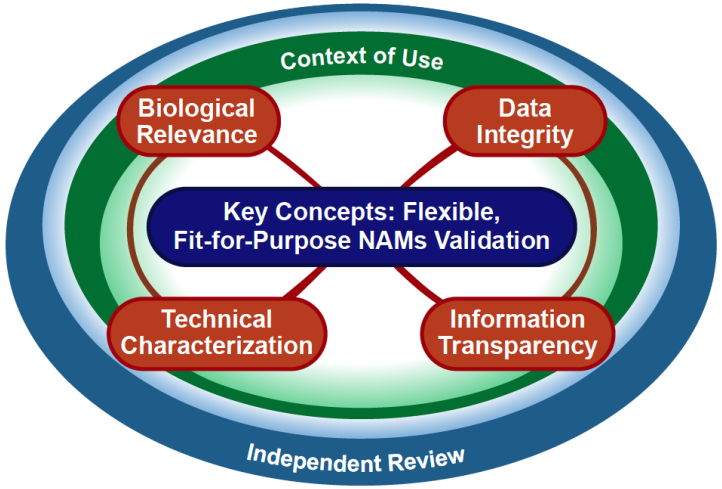
Insufficient detail vs too complex

(CS 2025-03, CS 2025-04, CS 2025-05)

Original Project Objectives and Vision

Progressing IATA for Systemic Toxicity: Examples, frameworks, and guidance to advance evaluation and application

1. Share and discuss outcomes and experiences.
2. Literature scan to characterize available approaches and data
3. Develop an IATA for Repeated-Dose Systemic Toxicity, including criteria for evaluating methods included within IATA.
4. Pilot application of the IATA with existing and novel case studies to demonstrate the variety of tools and use contexts.
5. Review insights from the pilot applications of the evaluation framework to available approaches and develop specific OECD guidance and/or recommend need for further evaluation.



ICCVAM Validation Report, Figure 1
(adapted from van der Zalm et al. 2022 Arch Tox)

One Pilot CS and Three CSs on Systemic Toxicity

Title: An Integrated Approach for Testing and Assessment for Systemic Risk Assessment

Versions

- IATA Framework Template – 0.1
- Workflow – 0.5
- Annex II – 0.1
- Annex IIIa – 0.1
- Annex IIIb – 0.1

Modifications to template

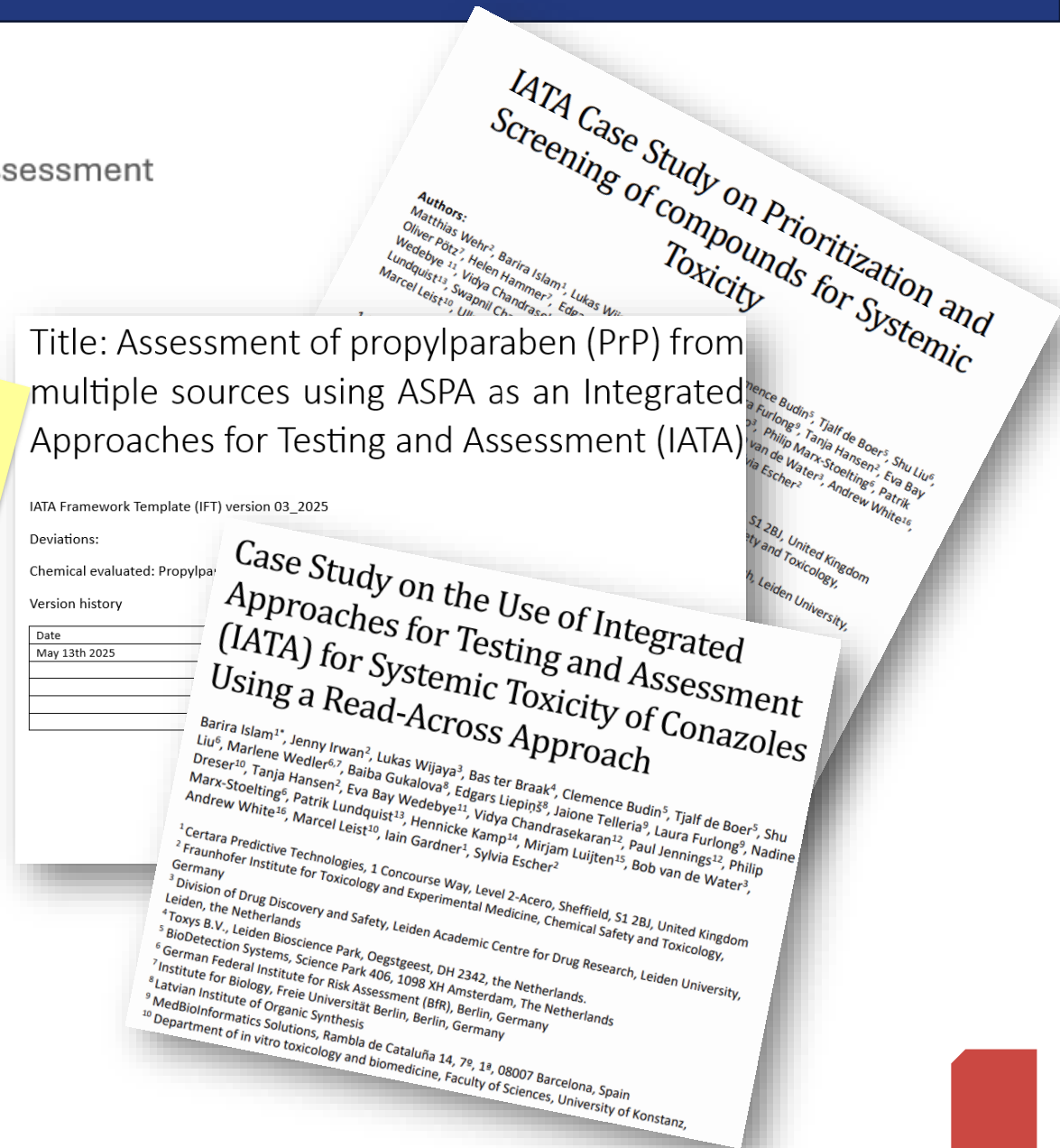
- Revised Information Source Table
- Annex I not used
- Annex II modified

Exemplar chemicals evaluated using this IATA Framework

- BP-4
- APCRA - ~200 chemicals

Initial observations:

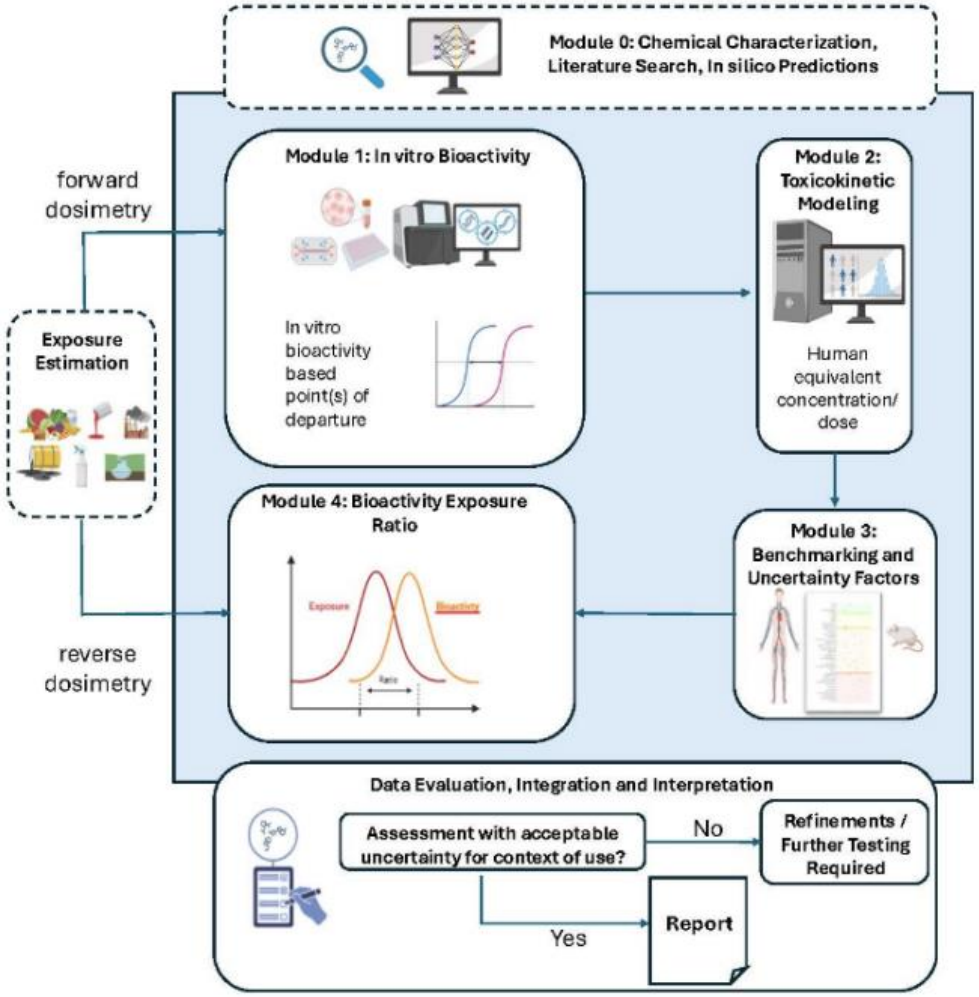
1. Same endpoint
2. Two different workflows
3. Both applicable to multiple regulatory decisions
4. Chemical agnostic?

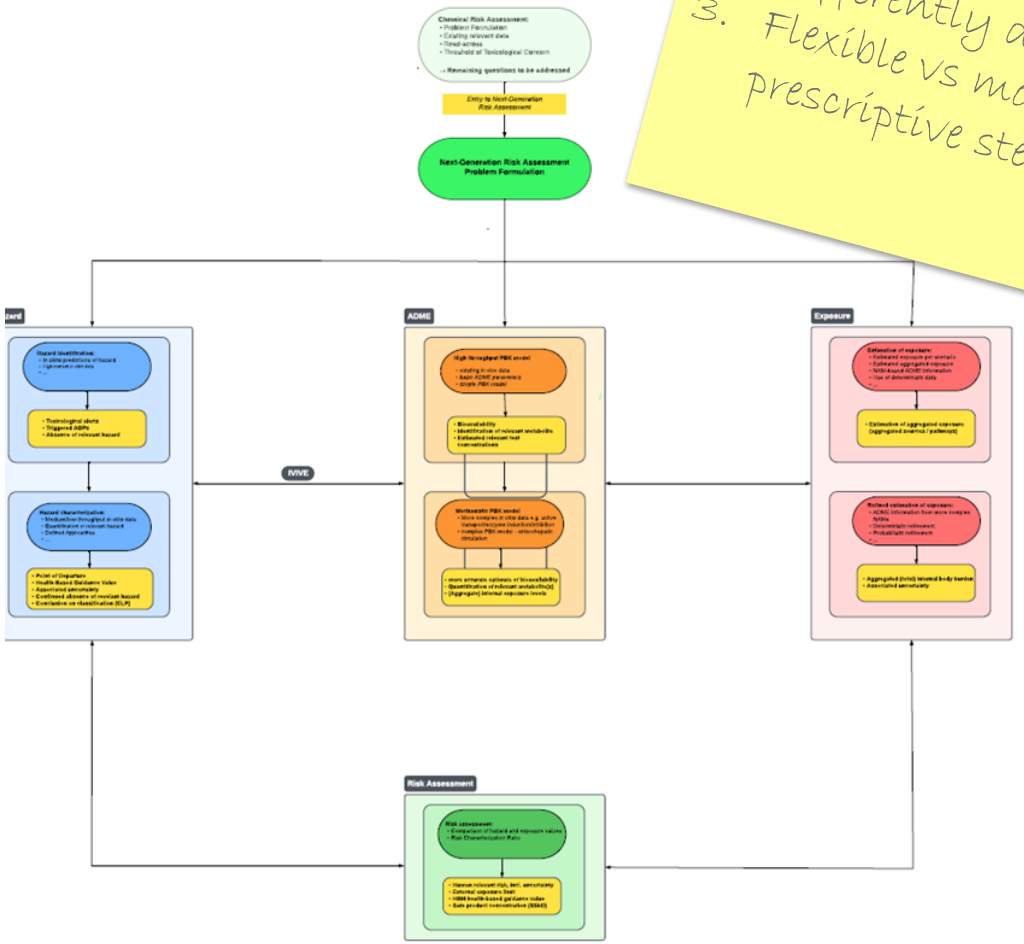


SysTox Workflow vs ASPA workflow

Initial observations:

1. Mostly same fundamental concepts: exposure driven, NAM-based
2. Similar modules differently defined
3. Flexible vs more prescriptive steps

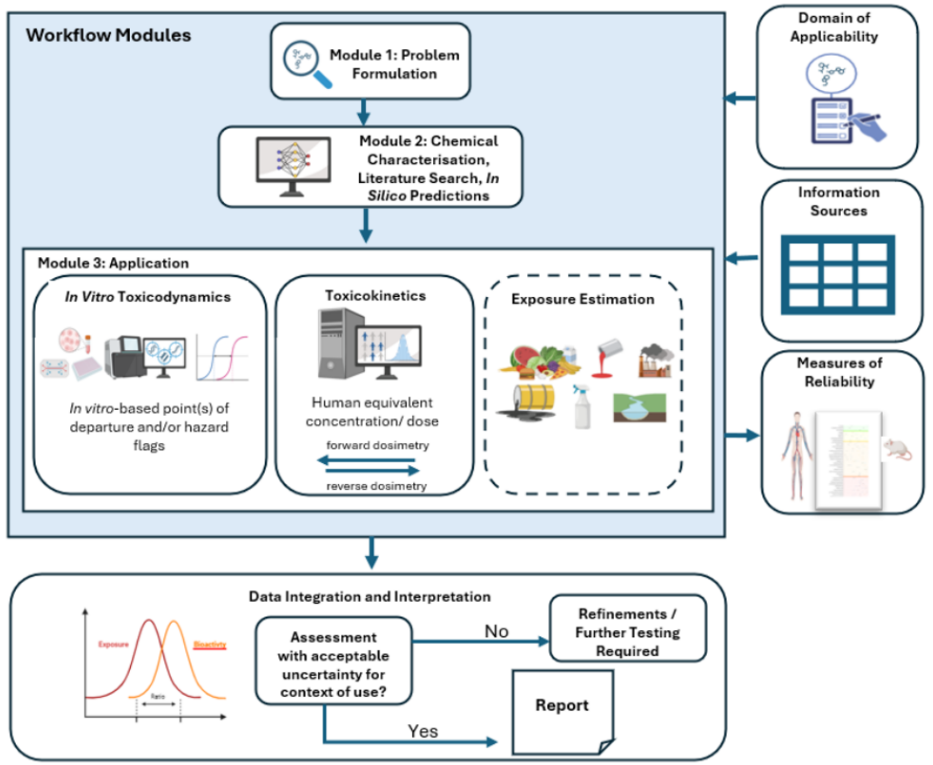




Activities

In combination ASPA case studies and the IATA project can both contributed to advancing the nto more general context-dependent guidance to start to bridge the gap between one-off case studies + general IATA – avoid the “it depends”

- **Workflow Harmonisation:** Aim prioritise areas for harmonise the OECD IATA and ASPA workflows, focusing on commonalities and integrating best practices.
- **Guidance Integration:** Review and incorporate relevant guidance and learnings from ASPA (including the handbook and assist tool) into the OECD IATA framework, ensuring consistency and leveraging existing materials
- **Benchmarking and Acceptance Criteria:** Develop conceptual criteria for regulatory acceptance and benchmarking of NAM-based risk assessments, considering variability and uncertainties in both animal and in vitro data.



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BETTER POLICIES FOR BETTER LIVES

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