Incorporating NAMs into a Tiered Assessment Framework for Agrochemical Metabolite Human Safety Assessment

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[1]Syngenta Crop Protection LLC, [2]Syngenta Canada Inc

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Background

Safety assessments and estimates of human exposure are required for both agrochemical active ingredients and their metabolites that may potentially form in the environment, crop, or livestock matrices.

- Current approaches for establishing toxicological reference values for metabolites are reliant upon structure-based grouping with limited application of read-across, which is challenging for the prediction of toxicological reference doses, and the conduct of time-intensive and low-throughput animal toxicology studies.
- The use of new approach methodologies (NAMs) to address the safety of agrochemical metabolites presents a promising opportunity to move away from traditional approaches towards more targeted methods which can be more directly applicable to humans.

Example of the Complexity with Metabolite Assessments

- Completion of metabolism studies often occurs towards the end of agrochemical research and development.
- Mammalian, plant, and environmental metabolism pathways may not overlap.

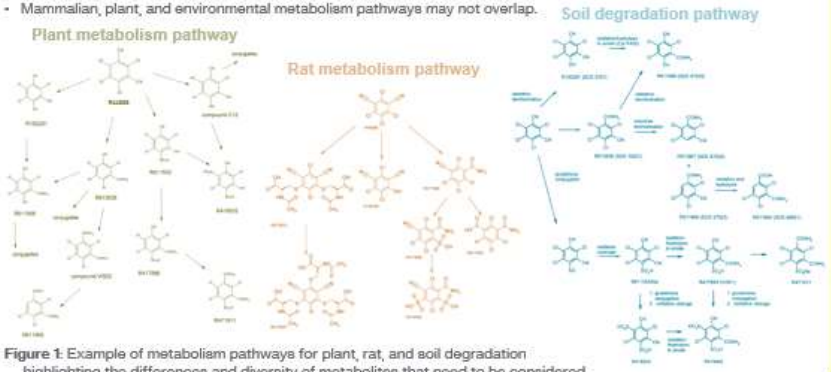


Figure 1: Example of metabolism pathways for plant, rat, and soil degradation highlighting the differences and diversity of metabolites that need to be considered.

Leveraging NAMs

- A "fit for purpose" tiered assessment framework focused on registration package application for determining agrochemical metabolite toxicity could be developed by leveraging existing knowledge supplemented by NAMs:
  - A decision tree style framework can optimally integrate knowledge from existing active ingredient studies as well as complementary *in vitro* and *in silico* data.
  - This framework supports the use of grouping based on commonality of biological perturbations.

Tiered Assessment Framework

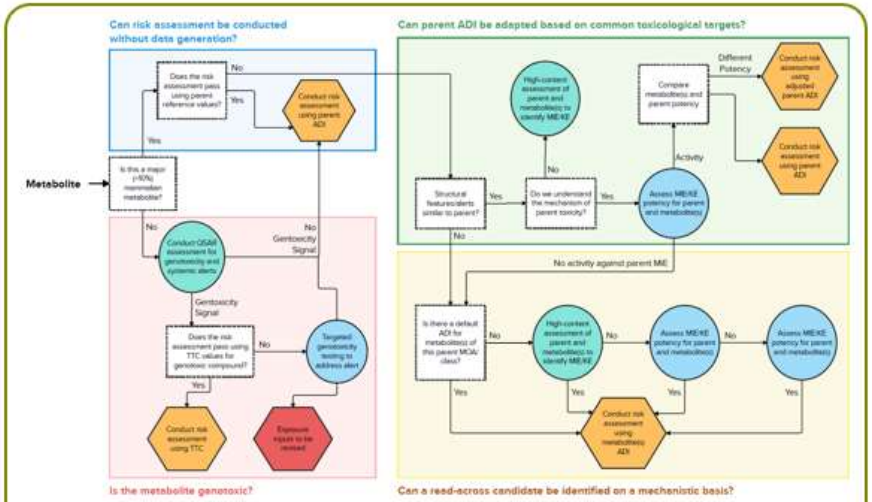


Figure 2: The decision-tree style tiered assessment framework integrates four fundamental approaches contextualized in this visualization by the four questions posed above/below the colored boxes. The goal is to use mode of action-based groupings to derive metabolite toxicity estimates. White boxes represent decision points (questions posed), hexagons are final approach for conducting risk assessment where yellow integrates existing data or NAMs whereas red would require animal testing, ovals represent NAM-based data generation wherein teel is an *in silico* approach and blue requires *in vitro* testing.

Summary & Next Steps

- Investigating interactions with common molecular targets allows for toxicity profiles to be extrapolated on the basis of mode of action (e.g., biologically-based read-across).
- This framework incorporates multiple NAM approaches, including toxicogenomics tools, structure-activity assessment, high-content *in vitro* screens, and targeted *in vitro* testing.
- Our aim with presenting this framework is to encourage future dialogue among industry and regulators to present scenarios by which NAMs can be selectively integrated with existing knowledge to derive toxicological reference values for risk assessment whilst maintaining transparency and reproducibility.

Background

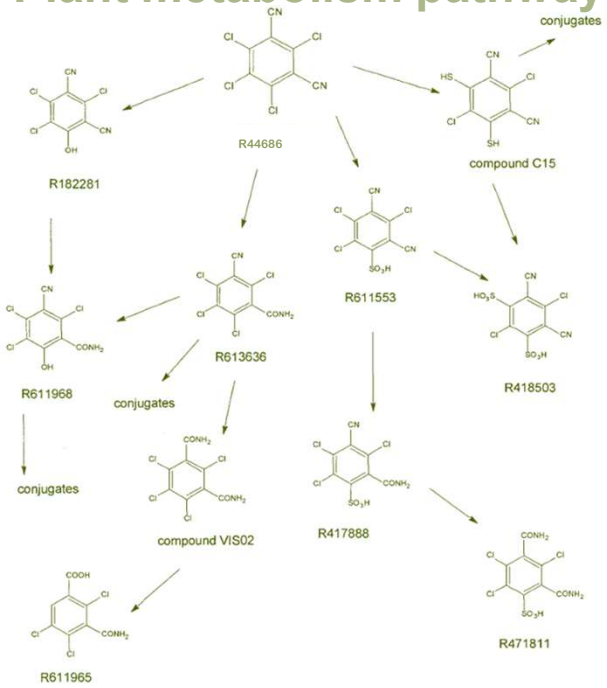
- Safety assessments and estimates of human exposure are required for agrochemical active ingredients and their metabolites
- Current approaches for establishing toxicological reference values for metabolites are reliant upon structure-based grouping
  - limited application of read-across
  - challenging for the prediction of toxicological reference doses
  - time-intensive and low-throughput animal toxicology studies
- Using new approach methodologies (NAMs) allows targeted testing that is more directly applicable to humans.

Example of Metabolite Assessment Complexity

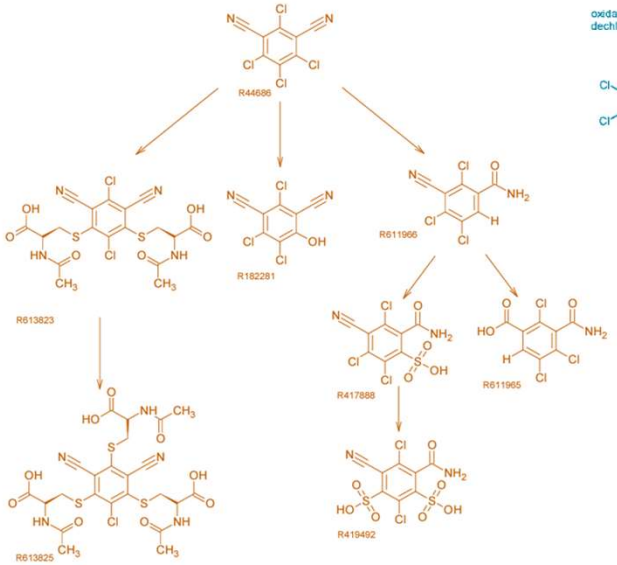
- Metabolism studies often done at end of agrochemical research and development
- Mammalian, plant, and environmental metabolism pathways may not overlap

Example of Metabolite Assessment Complexity

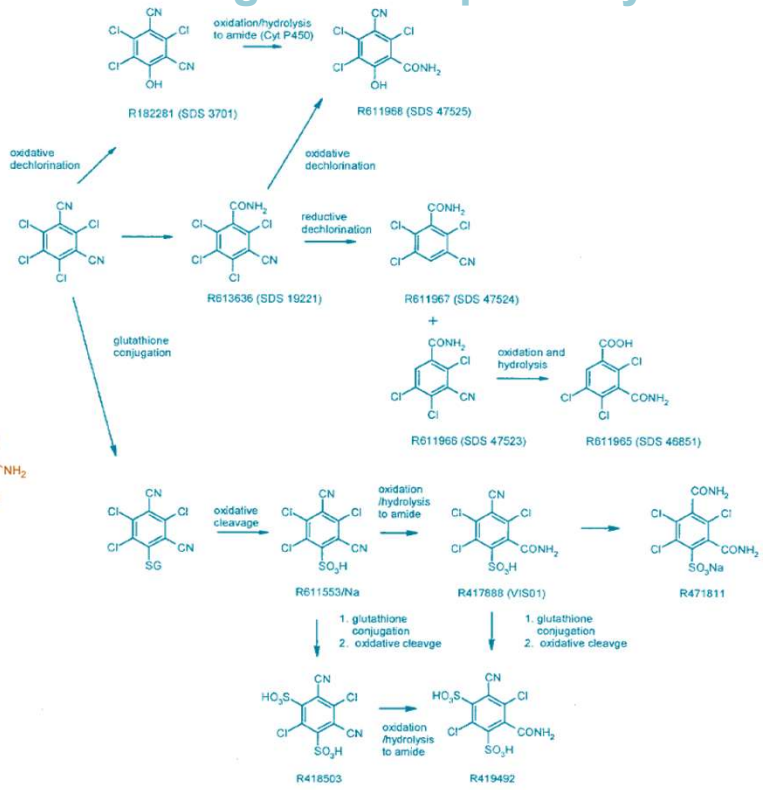
Plant metabolism pathway



Rat metabolism pathway



Soil degradation pathway



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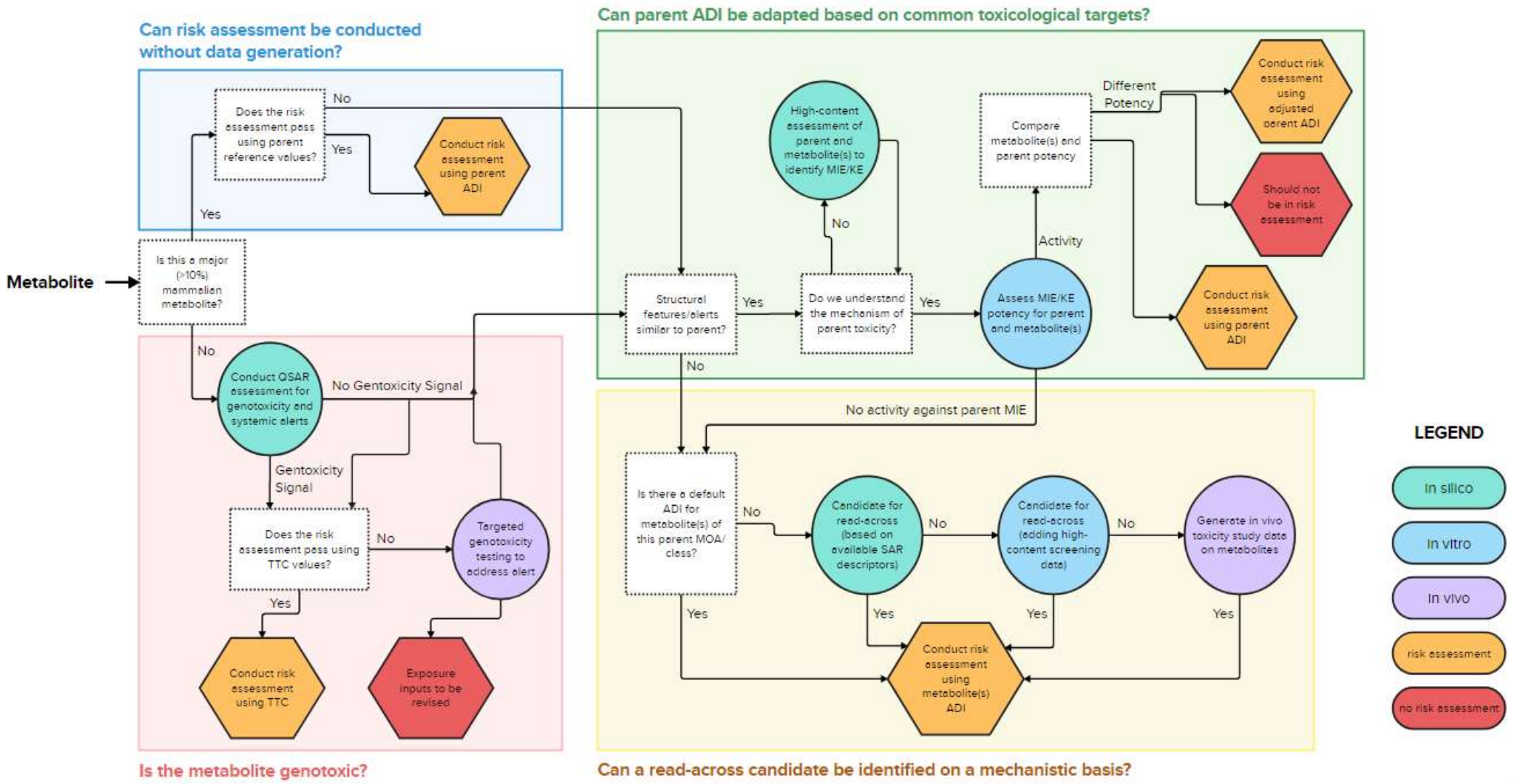
Tiered Framework Proposal

- A “fit-for-purpose” tiered assessment framework
- Focused on registration package application for determining agrochemical metabolite toxicity
- Developed by leveraging existing knowledge supplemented by NAMs

  - Decision tree style framework: can optimally integrate knowledge from existing active ingredient studies as well as complementary *in vitro* and *in silico* data
  - Supports the use of grouping based on commonality of biological perturbations


Can risk assessment be conducted without data generation?
Does the risk assessment pass using parent reference values?
No
Yes
Conduct risk assessment using parent ADI
Yes
Metabolite
Is this a major (>10%) mammalian metabolite?
No
Conduct QSAR assessment for genotoxicity and systemic alerts
No Gentoxicity Signal
Gentoxicity Signal
Does the risk assessment pass using TTC values?
No
Targeted genotoxicity testing to address alert
Yes
Conduct risk assessment using TTC
Exposure inputs to be revised
Is the metabolite genotoxic?
Can parent ADI be adapted based on common toxicological targets?
Structural features/alerts similar to parent?
Yes
No
High-content assessment of parent and metabolite(s) to identify MIE/KE
Do we understand the mechanism of parent toxicity?
Yes
No
Assess MIE/KE potency for parent and metabolite(s)
Activity
Compare metabolite(s) and parent potency
Different Potency
Conduct risk assessment using adjusted parent ADI
Should not be in risk assessment
Conduct risk assessment using parent ADI
No activity against parent MIE
Is there a default ADI for metabolite(s) of this parent MOA/ class?
No
Yes
Candidate for read-across (based on available SAR descriptors)
No
Yes
Candidate for read-across (adding high-content screening data)
No
Yes
Generate in vivo toxicity study data on metabolites
Yes
Conduct risk assessment using metabolite(s) ADI
Can a read-across candidate be identified on a mechanistic basis?
LEGEND
In silico
In vitro
In vivo
risk assessment
no risk assessment

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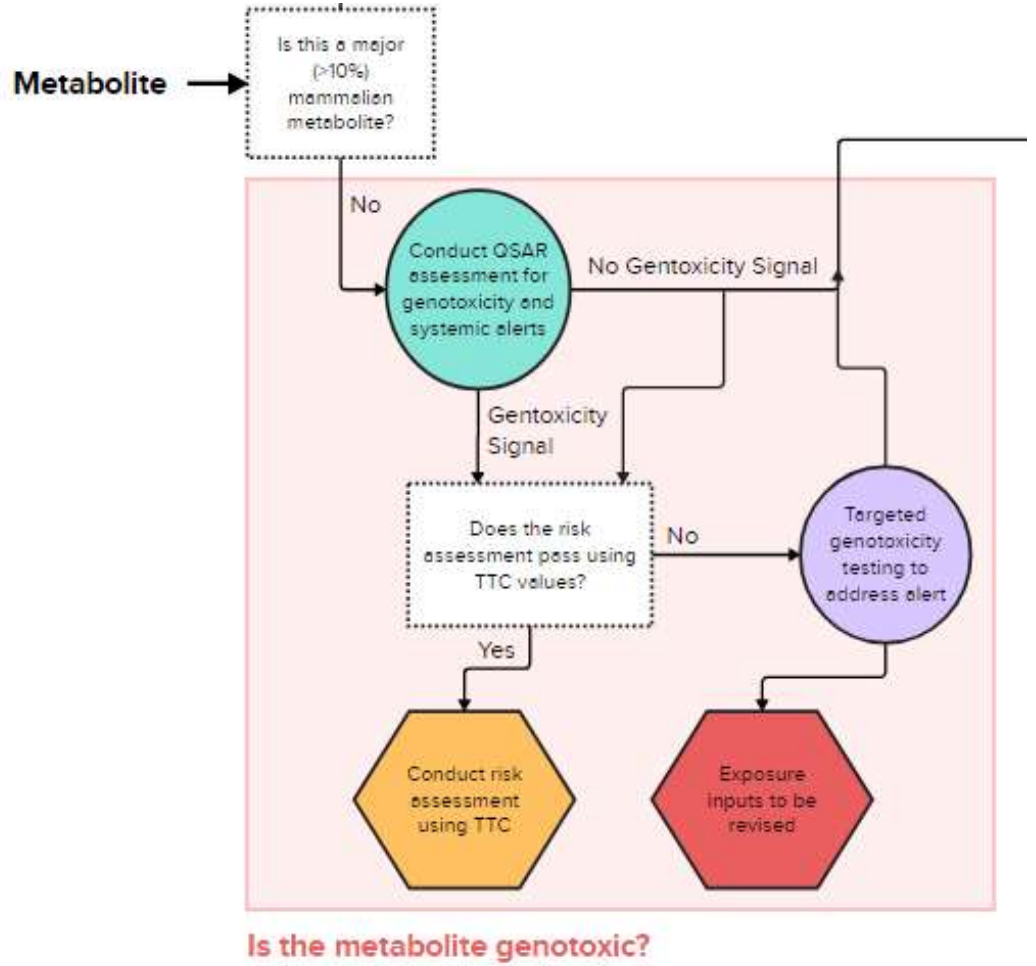
Genotoxicity

- Review genotoxicity potential for non-major metabolites
- Integration of in silico QSAR
- Consider TTC for these low-abundance metabolites
- Conduct targeted testing if neeeded



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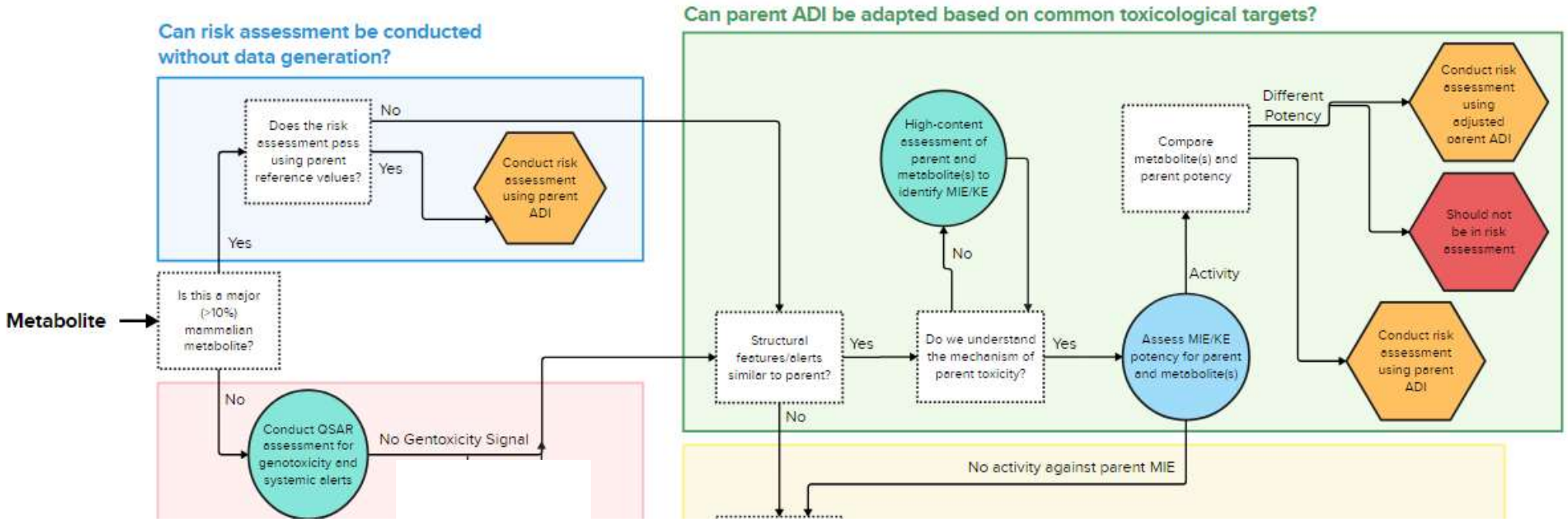
Comparison to Parent based on Toxicological Targets



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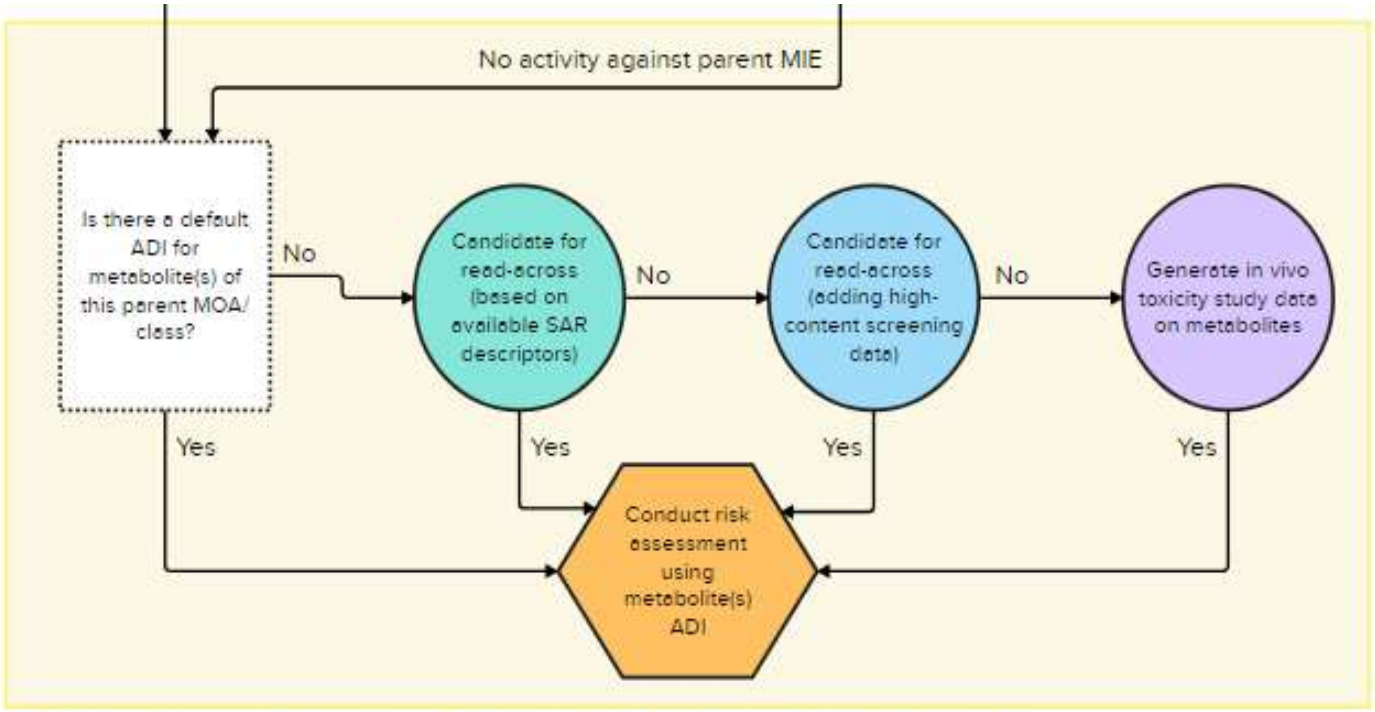
Read-Across to Leverage Other Scientifically Relevant Information



Can a read-across candidate be identified on a mechanistic basis?

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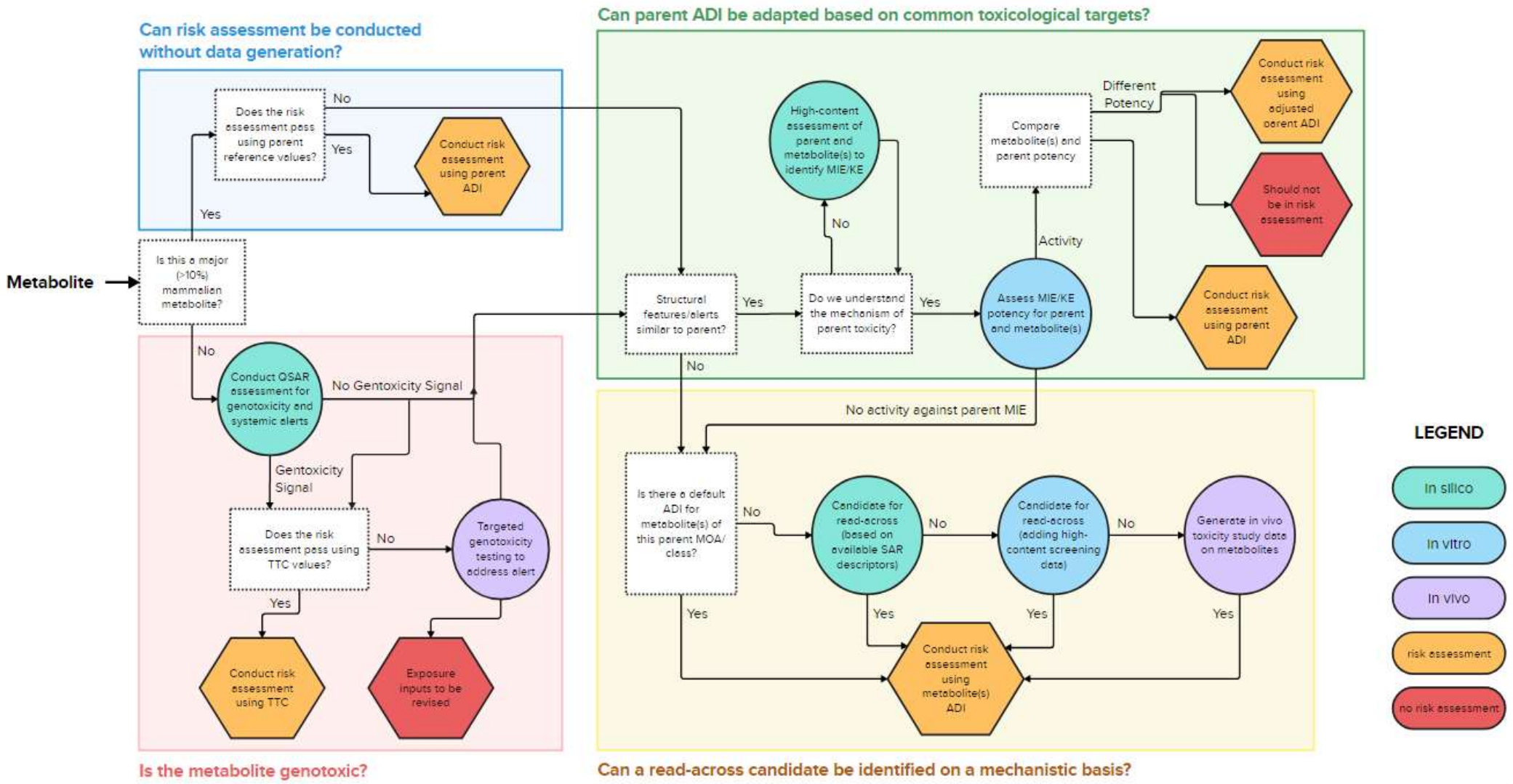
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