

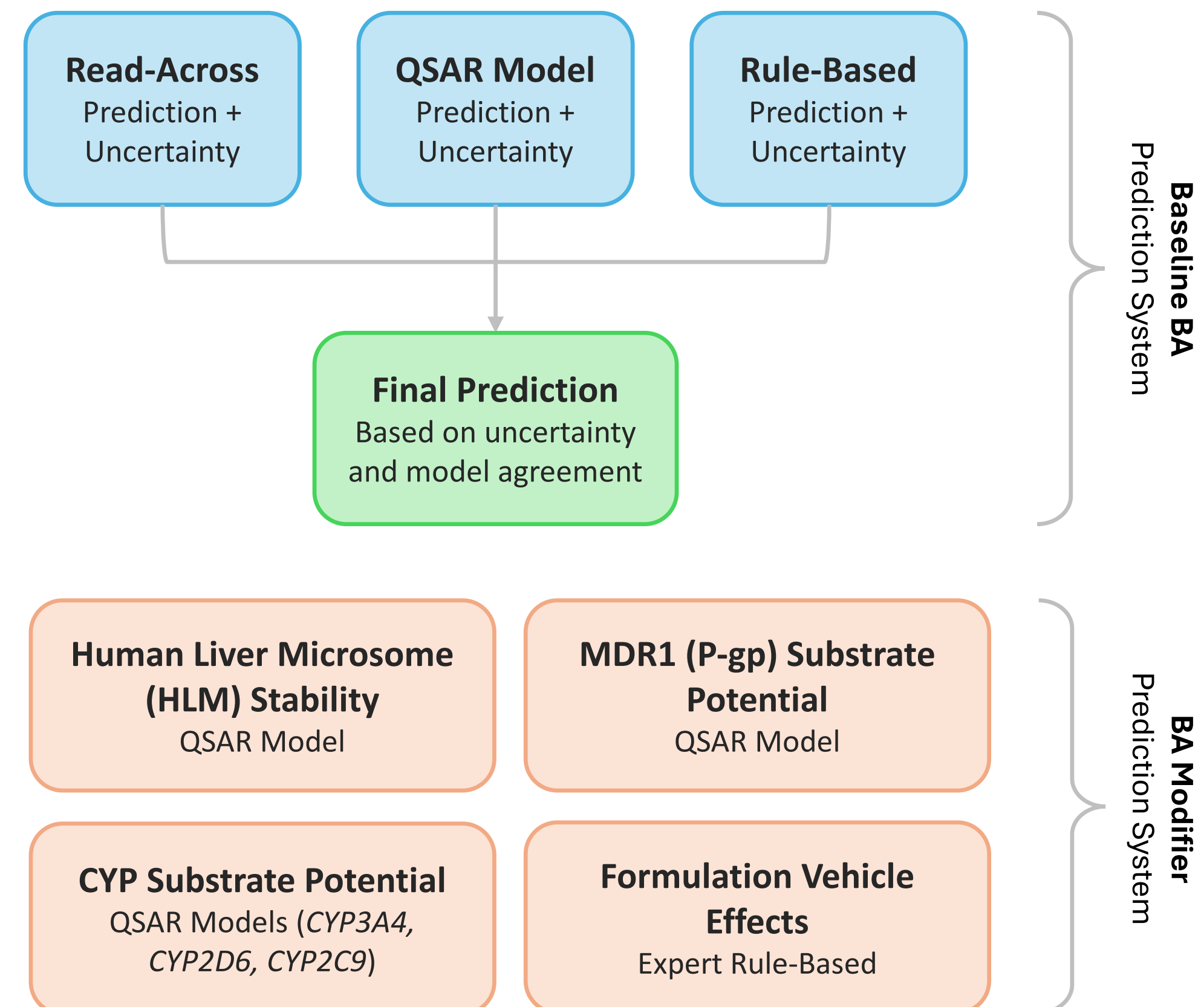
Background & Purpose

- **Definition of Oral Bioavailability:** Fraction of unchanged target compound reaching systemic circulation after oral ingestion.
- Predicting oral bioavailability (BA) of trace impurities, including leachables/extractables from container systems and medical devices, is critical for systemic risk assessment.
- Oral BA is influenced by physicochemical, metabolic, transport, and formulation factors.
- In silico tools to assess oral BA and vehicle effects are limited; single method-based models often lack robustness and interpretability.
- **Objective:** A transparent, uncertainty-aware multi-method framework to improve robustness and regulatory confidence in oral BA predictions.

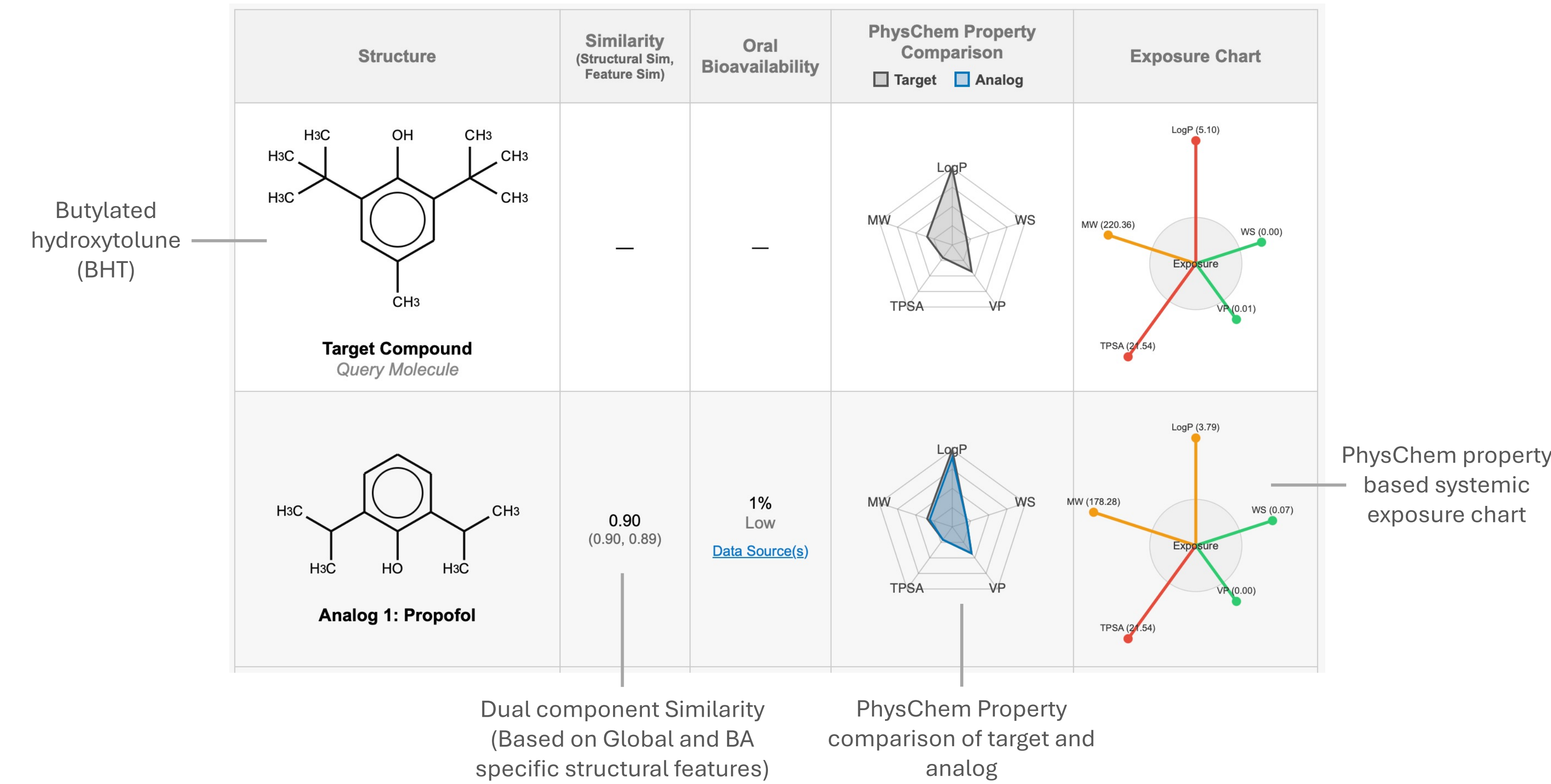
Data

Oral Bioavailability Data: 1594 compounds.¹ **Human Liver Microsomal Metabolism (HLM) Data:** 4637 compounds.² **CYP Substrate Datasets:** CYP3A4 (2601), CYP2D6 (2249), CYP2C9 (2209).³ **MDR1 (P-gp) Substrate Data:** 539 compounds.⁴

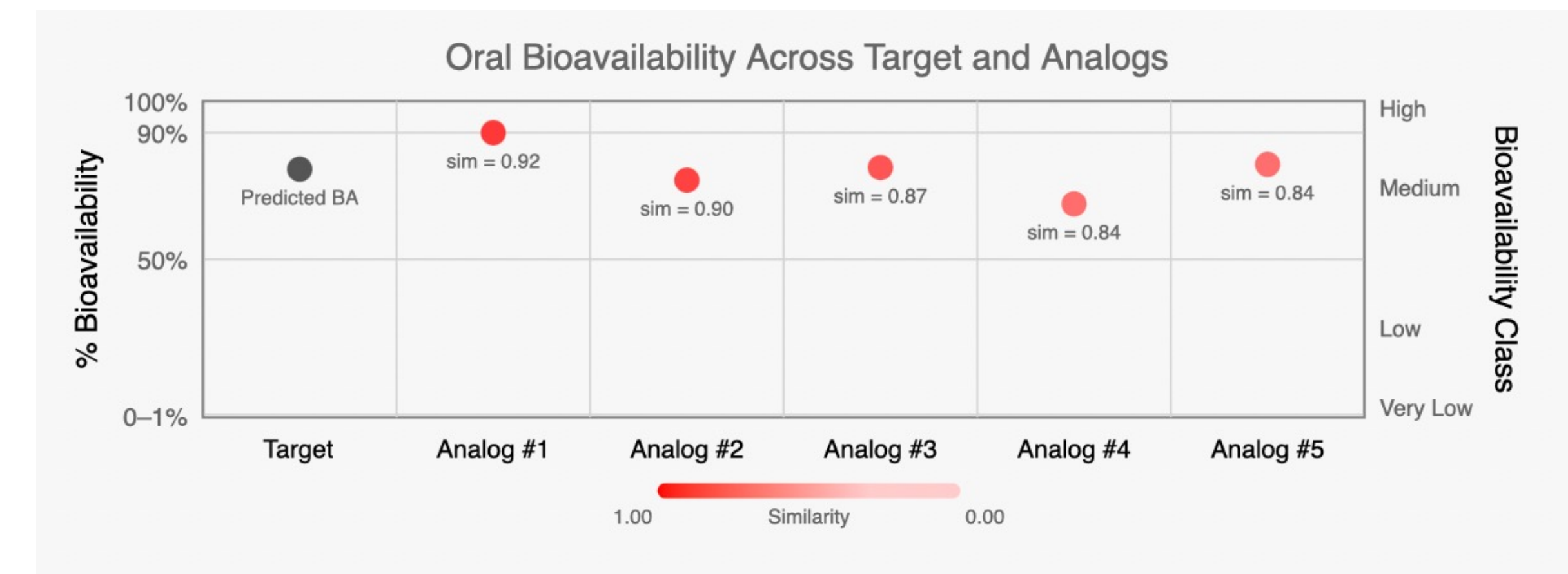
Method



Dual Similarity Read-Across: Structural + BA-Specific Features



Uncertainty Calculations in Read-Across



References

1. Collected and curated from public resources and research publications, 2025.
2. Li et al., Chem. Res. Toxicol., 2022, 35(9), 1614–24.
3. https://figshare.com/articles/dataset/Comprehensively-Curated_Dataset_of_CYP450_Interactions_Enhancing_Predictive_Models_for_Drug_Metabolism/26630515 (accessed: June 2025). License: <https://creativecommons.org/licenses/by/4.0/>
4. Sedykh, et al. Pharmaceutical Research 30, no. 4 (April 2013): 996–1007.

Expert Rules for Solvent Effects on Oral BA

Three Solvent Systems:

- Aqueous CMC suspension
- Aqueous co-solvent with ~5% DMSO
- Lipids or lipids + surfactants

Expert Rules are composed of:

- PhysChem properties of substance and vehicle, e.g., LogP, Water Solubility, Polar Surface Area
- Effects, e.g., small or large change in BA
- Reasoning phrase

Rules for lipid-based solvents:

If ...	then expect ...	Why
LogP > 5 and LogS < -2 and permeability OK	↑↑ Large increase possible	Highly lipophilic, poorly soluble compound drains via lymph when dissolved in lipid.
LogP > 5 and LogS < -2 but low permeability	↔ / ↓ Little benefit	Even if solubilised, permeability limits absorption.
3 < LogP ≤ 5 and -2 ≤ LogS < -1	↑ Modest improvement	Lipid dispersion enhances dissolution; partial lymphatic uptake.
LogP > 8 or TPSA > 120 Å² or HBD > 5	↔ / ↓ Little benefit	Too greasy (precipitation risk) or too polar (poor permeability).
Anything else	↔ Little effect	Molecule already soluble or too hydrophilic; lipid adds no advantage.

Case Studies

Diisobutyl Phthalate (DIBP)

Pred BA: Medium - Uncertainty: 23%

Experimental: Assumed ~100% oral absorption

Methods: RAX: Medium QSAR: Medium Rule-based: Low

Metabolism: HLM: Unstable; Substrate: CYP2D6

Vehicle effect: Modest improvement with lipid-based solvents

Comment: Bioavailability decreases due to first-pass metabolism.

Benzyl Alcohol

Pred BA: Medium - Uncertainty: 19%

Experimental: High oral absorption

Methods: RAX: Medium QSAR: Medium Rule-based: High

Metabolism: Substrate: CYP2D6

Vehicle effect: No meaningful change with different solvents

Comment: Rapid oxidation to benzaldehyde and benzoic acid, then hippuric acid.

Butylated Hydroxytoluene (BHT)

Pred BA: Low - Uncertainty: 33%

Experimental: High oral absorption

Methods: RAX: Low QSAR: Low Rule-based: Low

Metabolism: Predicted to be stable in HLM

Vehicle effect: Lipid vehicle: large increase possible via lymphatic uptake

Comment: First-pass metabolism; significant enterohepatic recirculation.

Lauro lactam

Pred BA: Medium - Uncertainty: 42%

Experimental: Limited water solubility (often associated with low absorption)

Methods: RAX: Medium QSAR: Very Low Rule-based: High

Metabolism: HLM: Unstable

Vehicle effect: 0.5% CMC; significant increase via rapid dissolution from micronized CMC suspension

Ethylene Glycol

Pred BA: Medium - Uncertainty: 16%

Experimental: EG and low-MW PEGs: high oral absorption

Methods: RAX: Medium QSAR: Medium Rule-based: High

Metabolism: Predicted to be stable in HLM

Vehicle effect: No major change was predicted

KEYS

RAX: Read-across prediction from structurally similar analogs

HLM: Human liver microsomes (in vitro metabolic stability)

CMC: Carboxymethylcellulose (suspending agent enhancing dissolution)

PEG: Polyethylene glycol

BA Tiers: Very Low (<1%), Low (≥1% and <50%), Medium (≥50% and <90%), High (≥90%)

Conclusions

- Orthogonal evidence streams reduce model bias and increase robustness.
- Supplementary models address mechanisms and scenarios not captured by baseline BA models.
- Explicit uncertainty quantification enables defensible regulatory decision-making.
- Designed to support weight-of-evidence assessments under regulatory review frameworks.
- **Limitation:** Does not directly account for the toxicity profiles of metabolites formed in vivo.

