Assessment of Systemic Toxicity of Parents and Metabolites from a Chemical Mixture Perspective Using a Read-Across Approach Leveraging Metabolism Databases and Decision Theory

J.F. Rathman[1,3], C. Yang[1,2], A Mostrag[1], B. Hobocienski[1], V. Ribeiro[1], T. Magdziarz[2]

[1]MN-AM, Columbus, OH; [2]MN-AM, Nuremberg, Germany; [3]Ohio State University, Columbus, OH

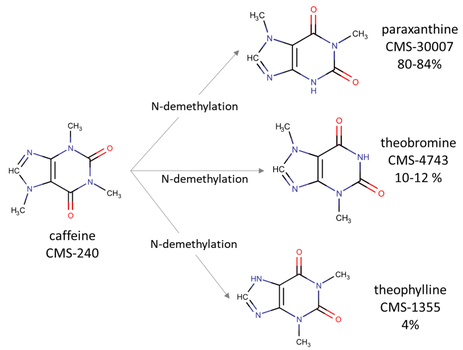
Abstract #3701
Poster board # P186

MOTIVATION

- Read-across approaches for parents and metabolites are considered from a mixture perspective.
- Compilation of evidence to support read-across includes Absorption, Distribution, Metabolism, and Excretion (ADME) profiles and biological assays, in addition to the conventional structure and molecular/physicochemical properties.
- Biological activities relevant to the toxicity of interest are captured by either assay activities or in silico methods such as QSAR or ML-hybrid structure rules.
- Various metabolites with estimated abundance are combined to give a quantitative read-across outcome with NOAEL bounds and uncertainties.

METABOLISM

Partial Metabolic Pathway of Caffeine: Human Oral



CONCLUSION

- Systemic/target organ NOAEL bounds were estimated to be 13-47 mg/kg-bw/day (at 95% confidence) for caffeine by read-across from three metabolites treated as a mixture.
- Analogue selection used structure, molecular properties, ADME properties, ER/AR assays, and ML-hybrid rules to quantify similarity to target.
- ML-hybrid rules allow for estimation of assay-based similarities when assay data for structures of interested is limited or unavailable. [Yang et al. submitted to Chem. Res. Toxicol. 2023]

ANALOG IDENTIFICATION, CHARACTERIZATION & ANALOG QUALITY (AQ)

$$AQ = \sqrt[N]{\prod_{i=1}^{N} (SimilarityMeasure)_i}$$

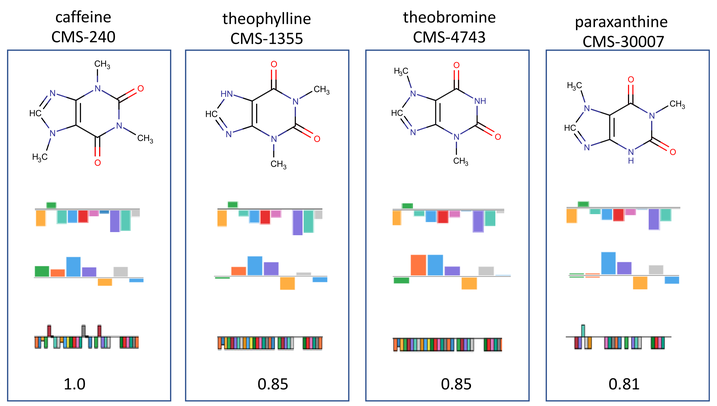
ToxPrints, MACCS Keys, RDKIT Molecular fingerprints (Tanimoto coefficients) → Structures (ToxPrints)

Rotational bonds, H-ACC, H-DON, Lipinski rule violations, MW, Complexity, TPSA, logP, Asphericity, Eccentricity. → Molecular Properties

Caco-2 Papp (cm/h), eFlux ratio, CLint_hepatic, Fraction bound, BBB, Oral intestinal abs %, Skin perm (logKp) → ADME Properties

AR, AR BLA, AR LUC, ER, ERa, ERb, ERaERa, ERa BLA, ERb BLA, ERa LUC, ERa TRANS, AhR, PR, PPAR → ER/AR Activity

ML-Hybrid Rule-based Similarity for ER/AR activities → Rule Similarity



MACHINE LEARNING (ML) – HYBRID RULES

Benefits of ML-Hybrid Rules

- Rules can be easily developed for a particular set of inventories or datasets with specific chemical classes
- ML-Hybrid rules can be developed for both positive and negative outcomes against the endpoints.

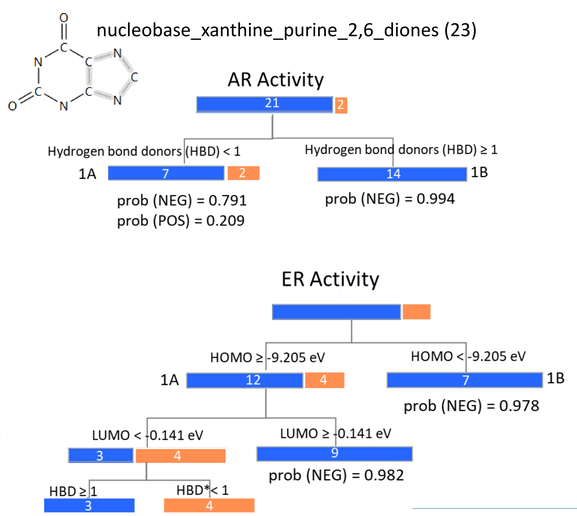
ER/AR Rules based on ToxCast/Tox21 Assays

- In vitro dataset contains 8593 compounds with more than 1400 assays
- Grouped by 24 modes of action and 43 mechanistic targets
- AR and ER assays were aggregated according to the MOA groups [Yang et al. Comp. Toxicol. 2023]
- In this study, 103 structures contain nucleobase, 23 structures are related to caffeine (purinedione class)
- Other 20 ML-Hybrid rules were also developed for ER/AR activities. [Yang et al. Chem. Res. Toxicol. 2023]

Rule-based Similarity

- ML-hybrid rules were also matched with structures. Each structure was represented by a vector of Bayes Factors, from which pairwise Euclidean similarities were calculated to be used in read-across. [Yang et al. Chem. Res. Toxicol. 2023]

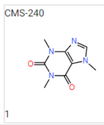
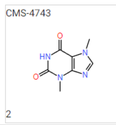
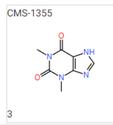
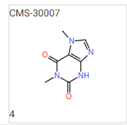
Recursive Partitioning Tree



*No bulky group (-CH2 >2) in pyrimidine or imidazole nitrogens

HOMO: Highest Occupied Molecular Orbital Energy (eV)
LUMO: Lowest Occupied Molecular Orbital Energy (eV)

ASSESSMENT SUMMARY REPORT

	Target	Analog	Analog	Analog
Compound Information				
Summary	CMS-240  1	CMS-4743  2	CMS-1355  3	CMS-30007  4
Chemical Similarity				
Tanimoto				
ToxPrint		0.87	0.93	1.00
Skyline Plots				
sky-prop				
Pearson similarity (0-1)		0.97	0.97	0.97
sky_adme				
Pearson similarity (0-1)		0.96	0.88	0.99
T0X21CAST				
Androgen Metabolism Process (4), Estrogen Metabolic Process (4)				
Euclidean similarity		0.49	0.49	0.46
Analog Quality	1.00 automatic	0.79 automatic	0.79 automatic	0.81 automatic
Repeated Dose Toxicity Data				
Rat RDT		☑	☑	☑
Study Type		Subchronic	Subchronic	Subchronic
Study Description	No Data	Mouse Oral - Gavage 14 weeks	Rat Oral - Gavage 14 weeks	Rat Oral - Diet 13 weeks
Study Quality [High, Med-High, Med, Med-Low, Low]		Med-High	Med-High	Med-Low
Study Quality (SQ) [Numeric 1-0]		0.9	0.9	0.85
Study Results - POD Info [Text]	No Data	NOAEL = 125 mkd	LOAEL = 37.5 mkd	NOAEL = 75 mkd
Study Result - chronic POD (mg/kg-bw/day)		41.7	4.17	25
Mouse RDT	☐	☐	☑	☐
Study Type			Subchronic	
Study Description	No Data		Mouse Oral - Gavage; 14 weeks	
Study Quality [High, Med-High, Med, Med-Low, Low]			Med-High	
Study Quality (SQ) [Numeric 1-0]			0.9	
Study Results - POD Info [Text]	No Data		NOAEL = 75 mkd	
Study Result - chronic POD (mg/kg-bw/day)			8.33	
RAX Reliability WOE				
Reliability per Analog		0.71	0.92	0.69
Reliability All Analogs	0.99	The read-across approach to repeated dose toxicity based on the selected analogs is justified by the high overall RAX reliability (99%). This value is obtained by a combination of AQ and SQ using Dempster-Shafer theory (DST).		
RAX Outcome				
95% CI from the selected analogues (averaging)	3 ≤ NOAEL ≤ 73			

caffeine (CMS-240)	Target	Relative amount	chronic NOAEL (mg/kg-bw/day)
theophylline (CMS-1355)	Analog-1	4%	4.17, 8.33
theobromine (CMS-4743)	Analog-2	10-12%	41.7
paraxanthine (CMS-30007)	Analog-3	80-84%	25

Weighted 95% CI NOAEL: 13.3 – 47.4 mg/kg-bw/day

3 – 73 mg/kg-bw/day (without weighting by abundance)

Contact: james.rathman@mn-am.com