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LabMol Laboratório de Planejamento de Fármacos e Modelagem Molecular

NTP Workshop on Predictive Models for Acute Oral Systemic Toxicity

NTP Collaboration on Modeling Acute Systemic Oral Toxicity: Results and Ideas

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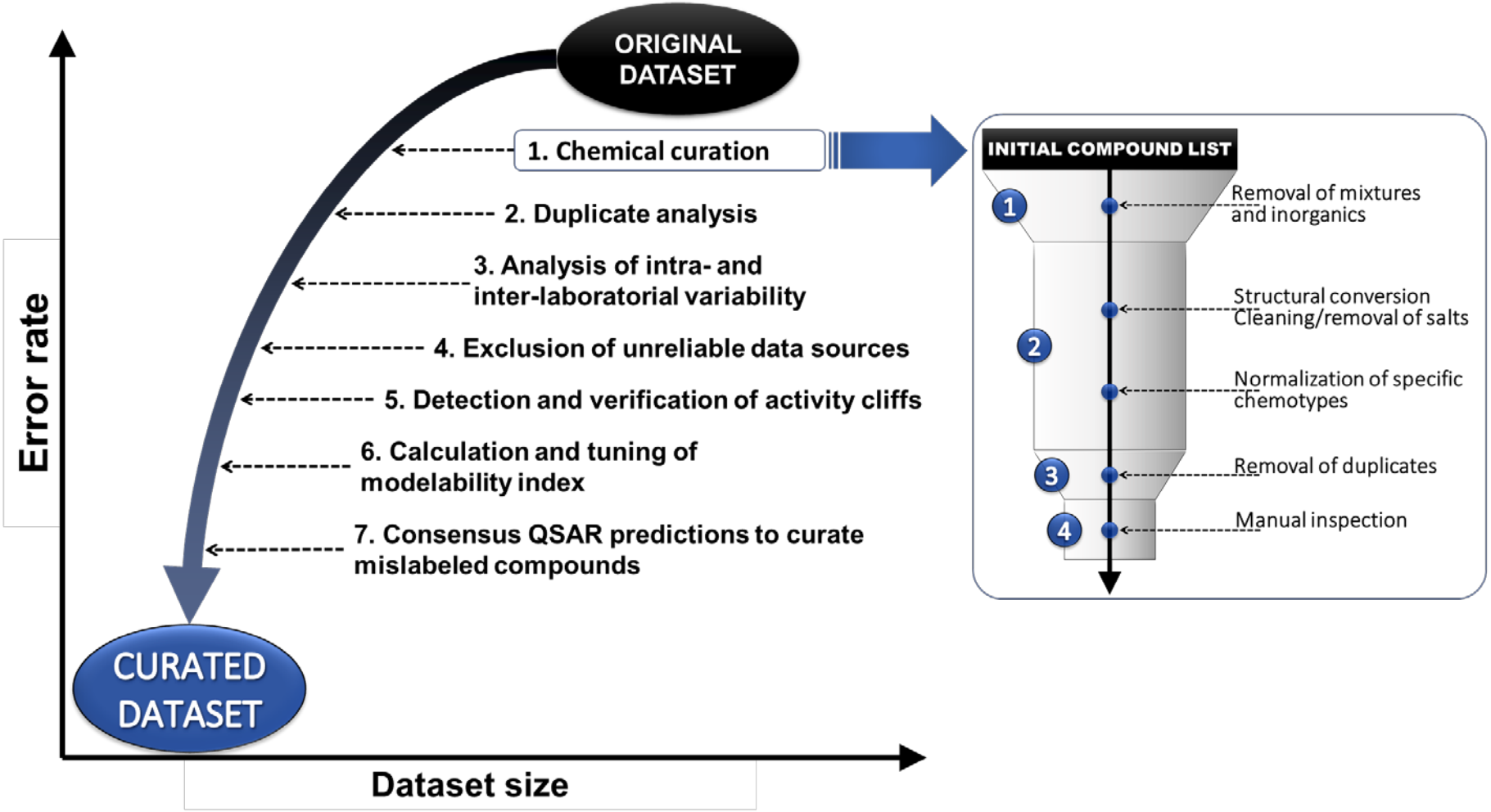
HOW TO SUCCEED IN COLLABORATION?

- Understanding of the problem;
- Use of additional data;
- Data curation;
- Rigorous External Validation;
- AD *vs.* 100% coverage;
- Consensus modeling;
- Experimental validation.

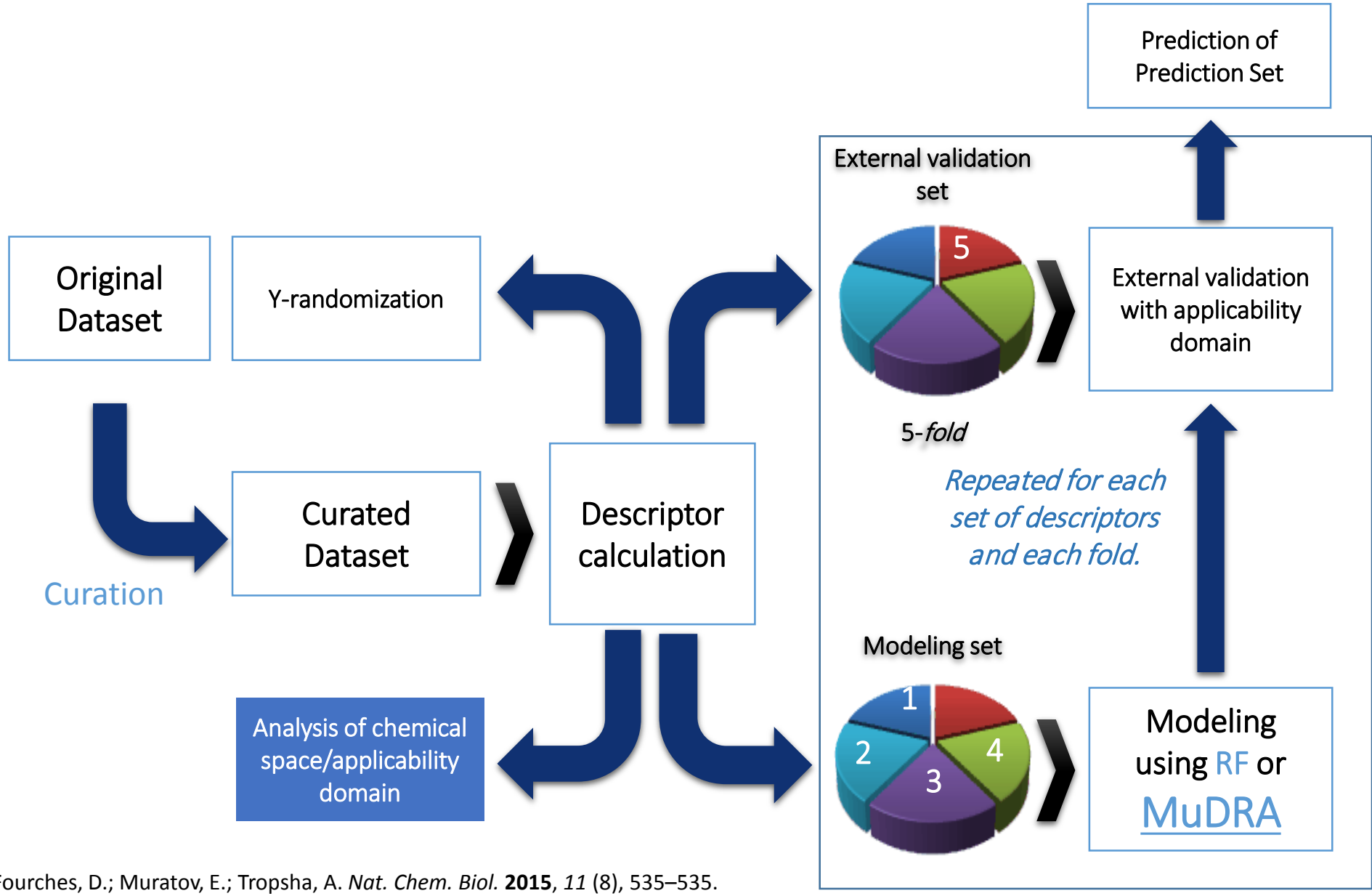
DATA CURATION



	Curated			
Original set	**VT**	**NT**	**GHS**	**EPA**
8,994	8,508	8,508	8,495	8,408

Fourches, D.; Muratov, E.; Tropsha, A. *J. Chem. Inf. Model.* **2016**, *56* (7), 1243–1252.
Fourches, D.; Muratov, E.; Tropsha, A. *Nat. Chem. Biol.* **2015**, *11* (8), 535–535.

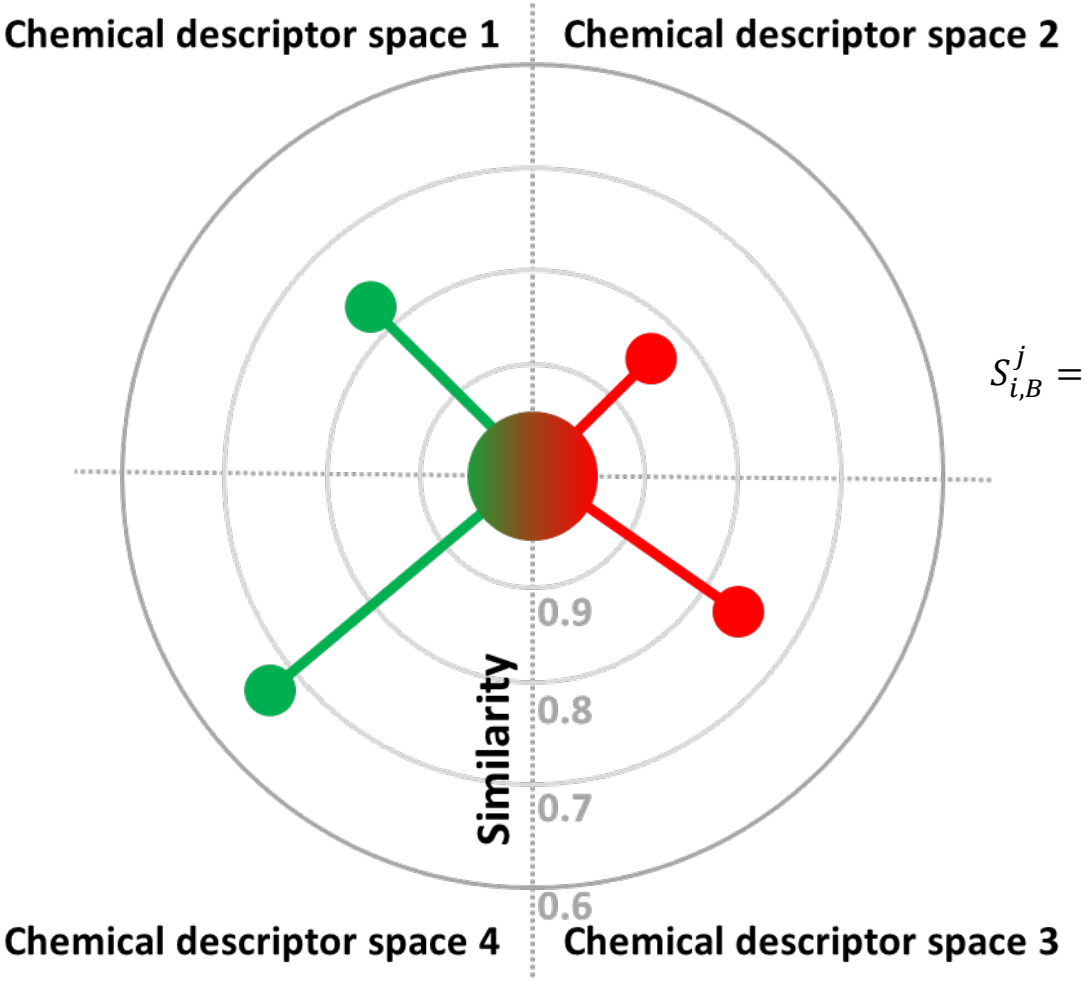
GENERAL WORFLOW



Fourches, D.; Muratov, E.; Tropsha, A. *Nat. Chem. Biol.* **2015**, *11* (8), 535–535.
Fourches, D.; Muratov, E.; Tropsha, A. *J. Chem. Inf. Model.* **2010**, *50*, 1189–1204
Tropsha, A. *Mol. Inform.* **2010**, *29*, 476–488.

Multi-Descriptor Read Across (MuDRA): a simple and transparent approach for developing accurate QSAR models

Vinicius M. Alves[a,b], Alexander Golbraikh[a], Stephen J. Capuzzi[a], Kammy Liu[c], Wai In Lam[c], Daniel Robert Korn[c], Diane Pozefsky[c], Carolina Horta Andrade[b], Eugene N. Muratov[a,d]*, Alexander Tropsha[a]*



$$S_{i,B}^{j} = 1 - d_{Jac} = \frac{\sum_{j=1}^{p_j} x_i^j x_{i,B}^j}{\sum_{j=1}^{p_j} \left(x_i^j\right)^2 + \sum_{j=1}^{p_j} \left(x_i^j\right)^2 - \sum_{j=1}^{p_j} x_i^j x_{i,B}^j}$$

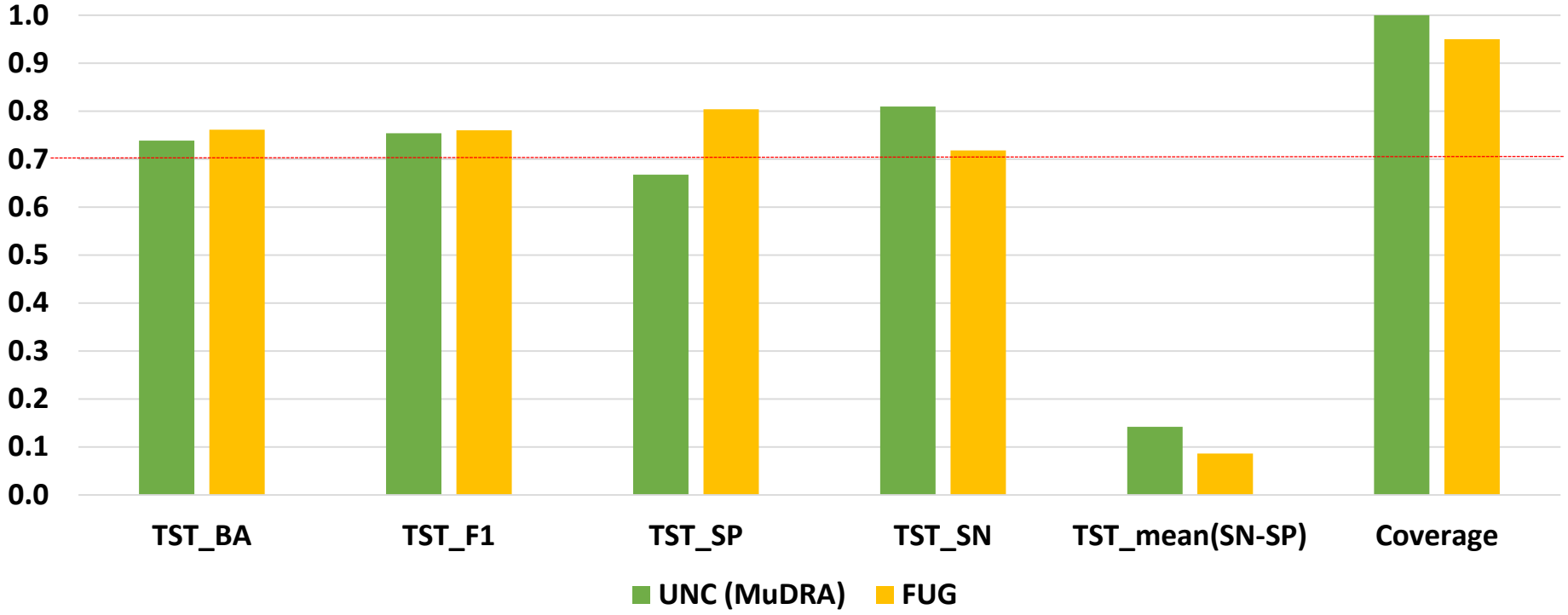
$$A_i^{pred,MCRA} = \frac{\sum_{j=1}^{D} \sum_{B_j=1}^{n_j} S_{i,B_j}^{j} A_{i,B_j}^{j}}{\sum_{j=1}^{D} \sum_{B_j=1}^{n_j} S_{i,B_j}^{j}}$$

MuDRA *vs*. CERAPP MODELS

Agonist (n=6,319)			
Model	CCR	Sensitivity	Specificity
CERAPP (n = 5)	0.73 (± 0.05)	0.51 (± 0.13)	0.95 (± 0.05)
MuDRA	0.74	0.65	0.83
Antagonist (n=6,532)			
Model	CCR	Sensitivity	Specificity
CERAPP (n = 4)	0.53 (± 0.02)	0.11 (± 0.09)	0.95 (± 0.05)
MuDRA	0.52	0.05	0.99
Binding (n=7,283)			
Model	CCR	Sensitivity	Specificity
CERAPP (n = 9)	0.57 (± 0.02)	0.27 (± 0.11)	0.85 (± 0.08)
MuDRA	0.58	0.35	0.81

CERAPP compounds are provided by Dr. Mansouri.

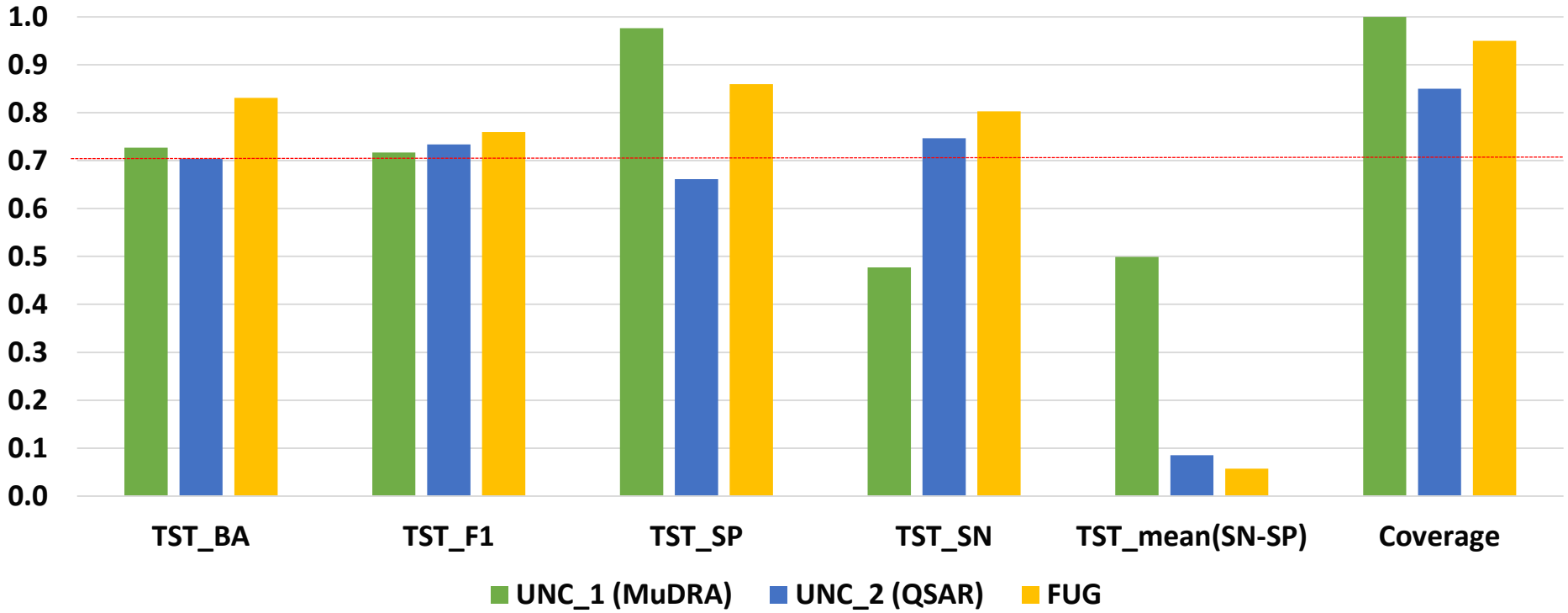
NON TOXIC MODELS



	UNC (MuDRA)	FUG
Descriptors	SiRMS, DRAGON, Morgan, RDKit	MACCS
Algorithm	MuDRA	RANDOM FOREST
No. of compounds in training set	4,834 toxic 3,661 not very toxic	2,298 toxic 2,298 not very toxic

The Statistics is provided to participants by Dr. Mansouri.

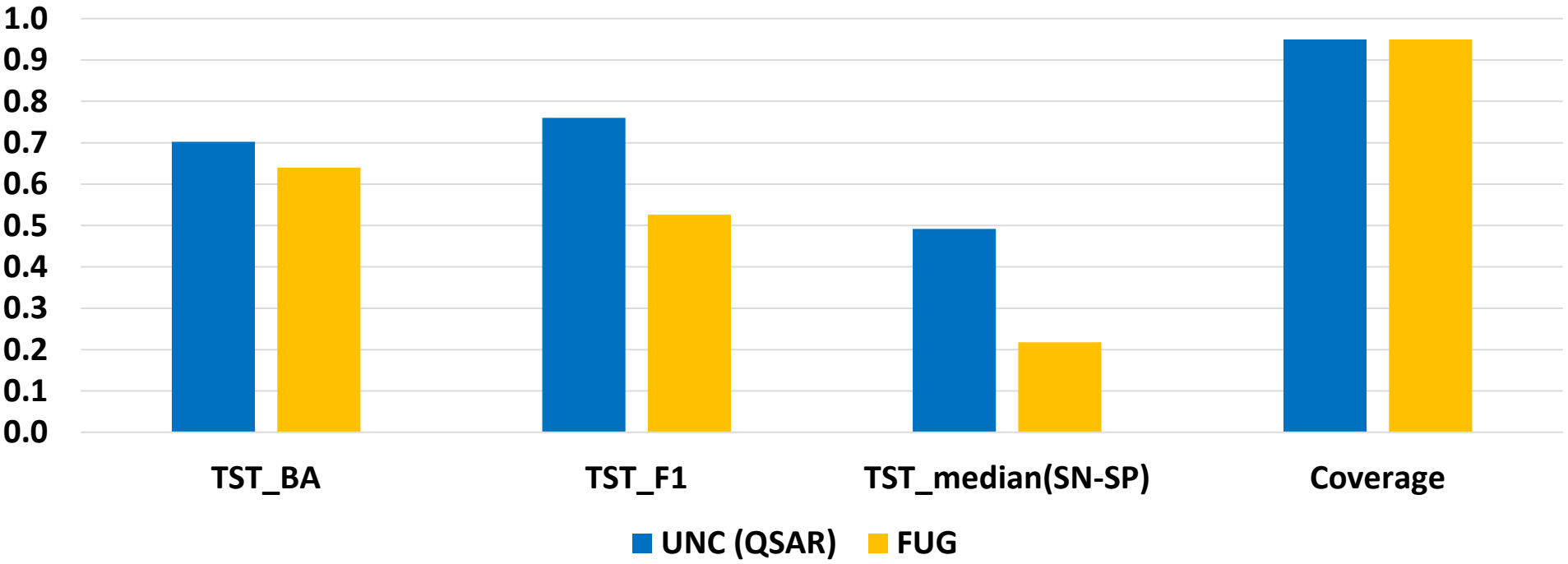
VERY TOXIC MODELS



	UNC_1 (MuDRA)	UNC_2 (QSAR)	FUG
Descriptors	SiRMS, DRAGON, Morgan, RDKit	DRAGON	MACCS
Algorithm	MuDRA	RANDOM FOREST	RANDOM FOREST
No. of compounds in training set	716 very toxic 7,790 not very toxic	385 very toxic 385 not very toxic	572 very toxic 572 not very toxic

The Statistics is provided to participants by Dr. Mansouri.

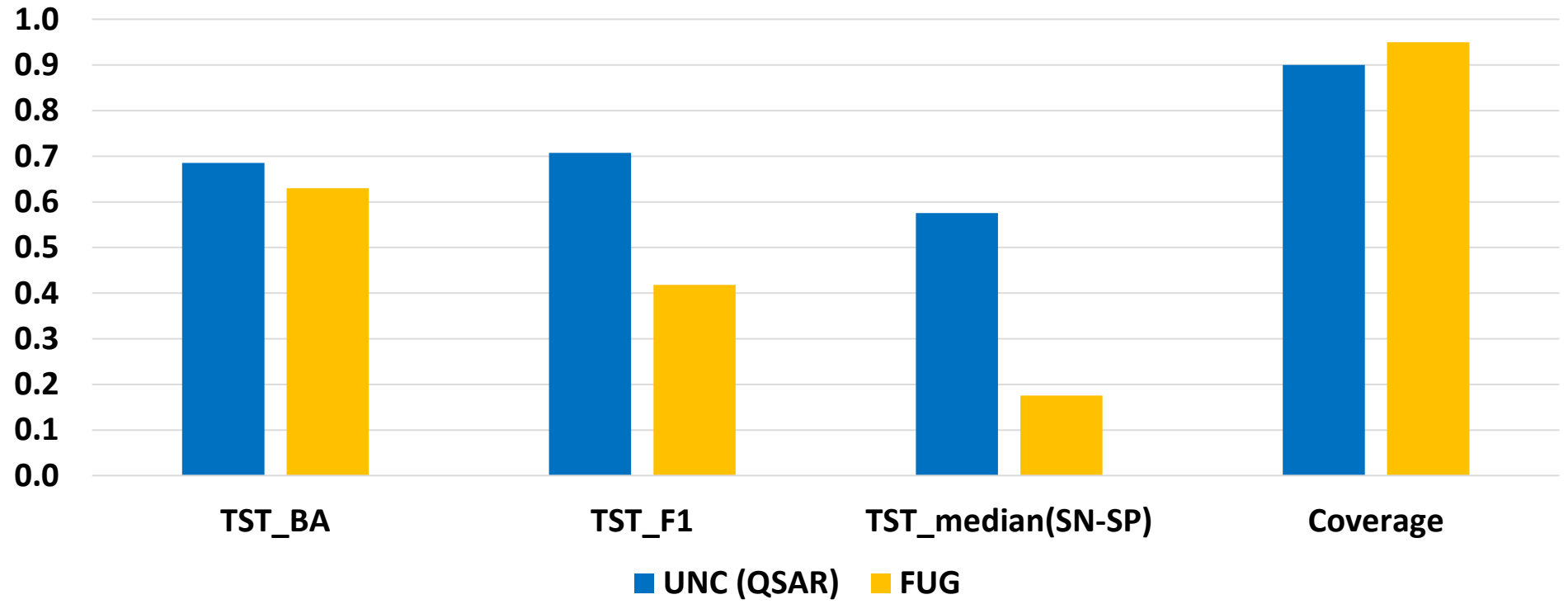
EPA MODELS



	UNC (QSAR)	FUG
Descriptors	SiRMS, DRAGON, Morgan, RDKit	MACCS
Algorithm	MuDRA	RANDOM FOREST
No. of compounds in training set	464 extreme (cat. I) 1,099 strong (cat. II) 5,840 moderate (cat. III) 1,005 non-toxic (cat. IV)	1,048 extreme/strong (cat. I and II) 1,048 moderate (cat. III) 1,048 non-toxic (cat. IV)

The Statistics is provided to participants by Dr. Mansouri.

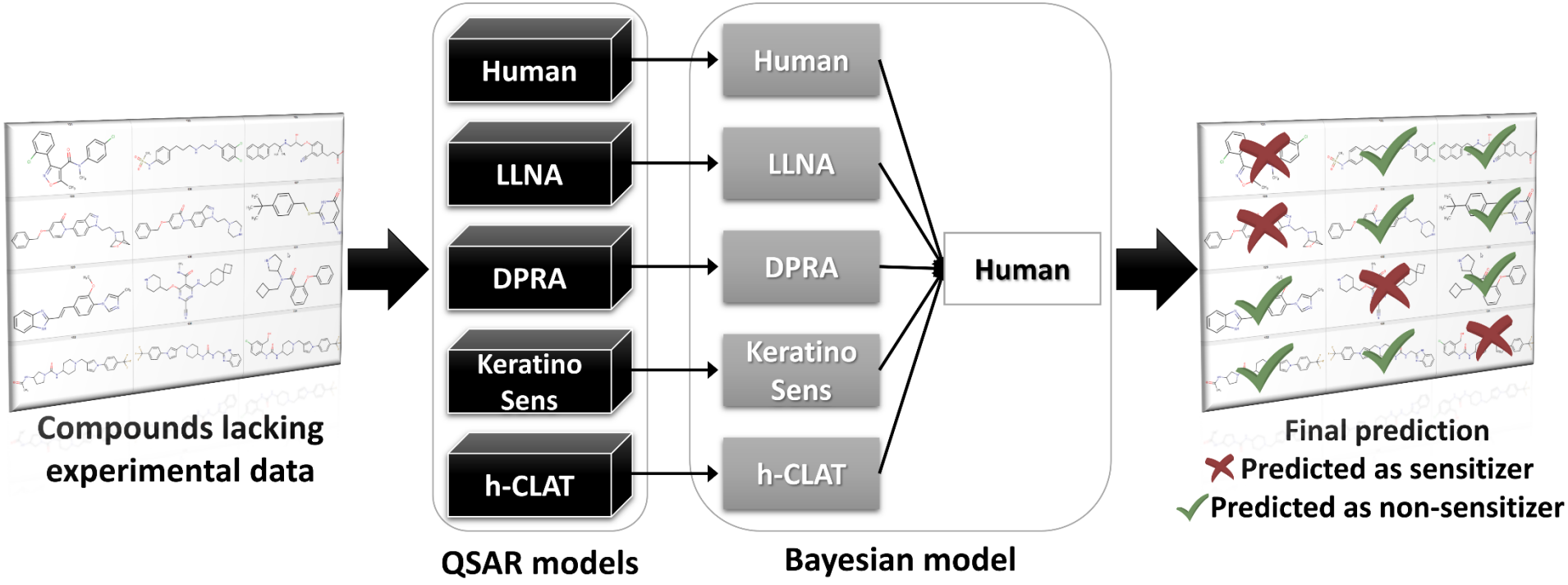
GHS MODELS



	UNC (QSAR)	FUG
Descriptors	SiRMS, DRAGON, Morgan, RDKit	MACCS
Algorithm	MuDRA	RANDOM FOREST
No. of compounds in training set	458 extreme (cat. I) 334 strong (cat. II) 70 moderate (cat. III) 3,297 non-toxic (cat. IV)	512 extreme/strong (cat. I and II) 512 moderate (cat. III) 512 non-toxic (cat. IV)

The Statistics is provided to participants by Dr. Mansouri.

SMART CONSENSUS MODELING



ACS Sustainable Chemistry & Engineering

Perspective

Cite This: *ACS Sustainable Chem. Eng.* 2018, 6, 2845−2859

pubs.acs.org/journal/ascecg

A Perspective and a New Integrated Computational Strategy for Skin Sensitization Assessment

Vinicius M. Alves,[†,‡] Stephen J. Capuzzi,[†] Rodolpho C. Braga,[‡] Joyce V. B. Borba,[‡] Arthur C. Silva,[‡] Thomas Luechtefeld,[§] Thomas Hartung,[§] Carolina Horta Andrade,[‡] Eugene N. Muratov,[*,†,∥] and Alexander Tropsha[*,†]

FINAL REMARKS

- Correct identification and formulation of a problem is a must;
- Use of additional data is extremely helpful;
- Data curation and rigorous external validation is critical;
- MuDRA is a simple, fast, and reliable approach that yields similar accuracy with complex modeling ensembles with 100% coverage of the prediction set;
- We recommend use of AD for single models but 100% coverage for final consensus ensemble;
- Comparison of the accuracy of the models must be made using the same compounds only;
- Building smart consensus model is recommended – let the models help each other;
- Only experimental validation could demonstrate predictivity and utility of a model.

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- Organizers of NTP Collaboration;
- Organizers of the Workshop;
- Kamel Mansouri (NICEATM);
- Nicole Kleinstreuer (NICEATM);
- Alexey Zakharov (NCATS);
- Denis Fourches (NCSU).

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JOURNAL OF CHEMICAL INFORMATION AND MODELING

Application Note

pubs.acs.org/jcim

Chembench: A Publicly Accessible, Integrated Cheminformatics Portal

Stephen J. Capuzzi,[†] Ian Sang-June Kim,[†] Wai In Lam,[‡] Thomas E. Thornton,[†] Eugene N. Muratov,[†] Diane Pozefsky,[*,‡] and Alexander Tropsha[*,†,‡]

[†]Laboratory for Molecular Modeling, Division of Chemical Biology and Medicinal Chemistry, UNC Eshelman School of Pharmacy, and [‡]Department of Computer Science, University of North Carolina, Chapel Hill, North Carolina 27599, United States

https://chembench.mml.unc.edu/mudra/

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Food and Chemical Toxicology 112 (2018) 526–534

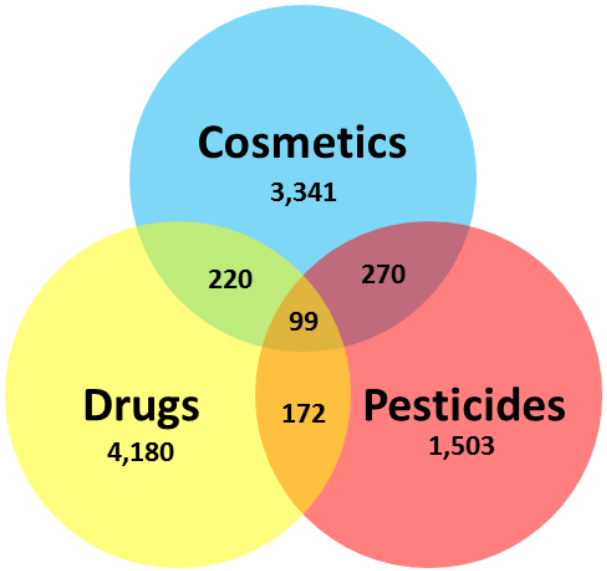
Contents lists available at ScienceDirect

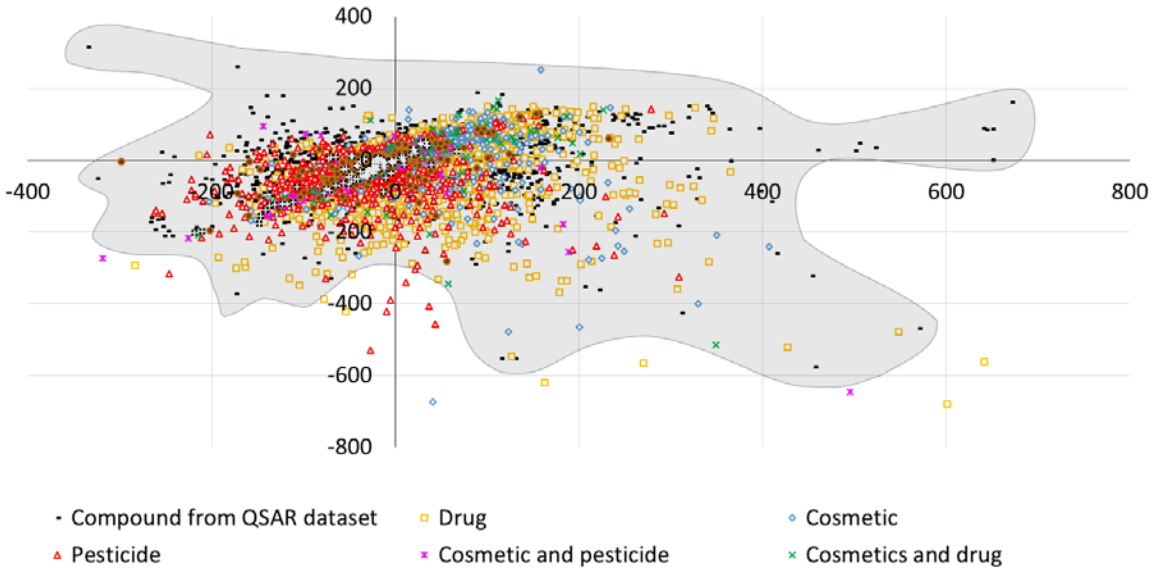
Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Chemical toxicity prediction for major classes of industrial chemicals: Is it possible to develop universal models covering cosmetics, drugs, and pesticides?

Vinicius M. Alves [a, b], Eugene N. Muratov [a, c], Alexey Zakharov [d], Nail N. Muratov [c], Carolina H. Andrade [b], Alexander Tropsha [a, *]





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Implementation of QSAR models for use of the scientific community

JOURNAL OF CHEMICAL INFORMATION AND MODELING

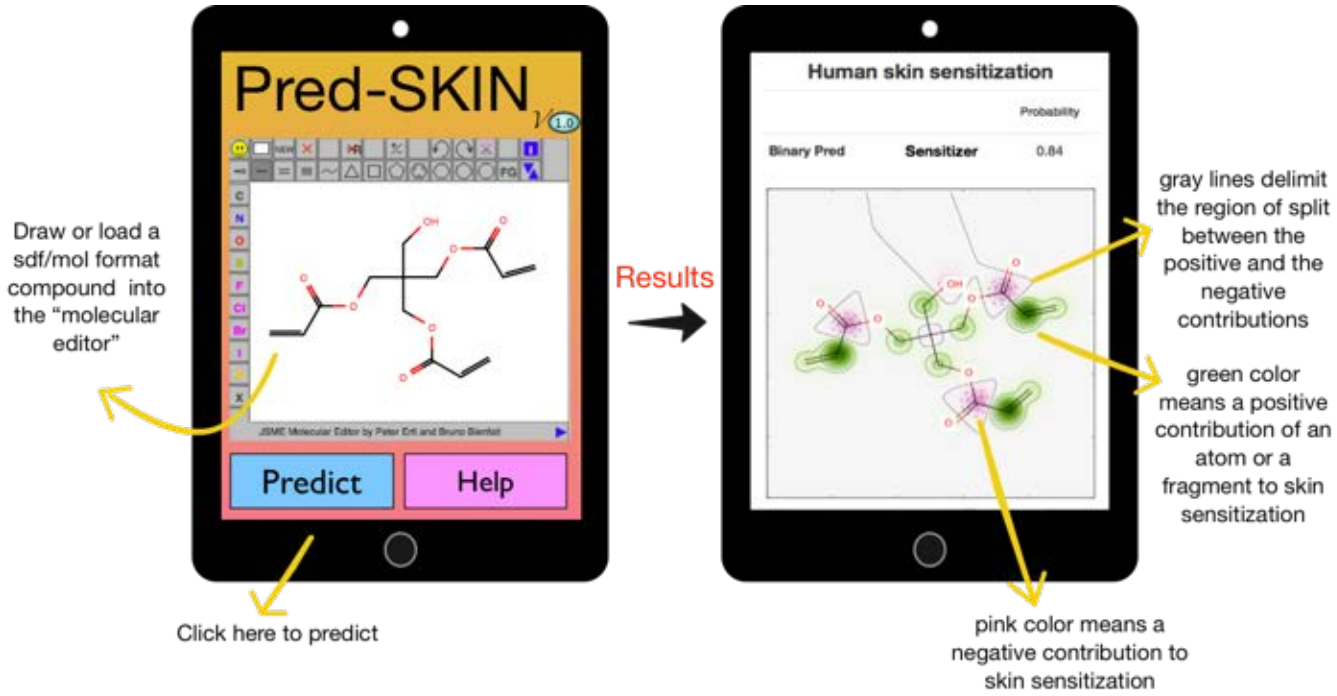
Application Note

pubs.acs.org/jcim

Pred-Skin: A Fast and Reliable Web Application to Assess Skin Sensitization Effect of Chemicals

Rodolpho C. Braga,[†,○] Vinicius M. Alves,[†,‡,○] Eugene N. Muratov,[‡,§] Judy Strickland,[∥] Nicole Kleinstreuer,[⊥] Alexander Trospsha,[‡] and Carolina Horta Andrade*[,†]

www.labmol.com.br/predskin



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NIH NIEHS