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Computational Molecular Modeling Methods Applied to Screening for Toxicity

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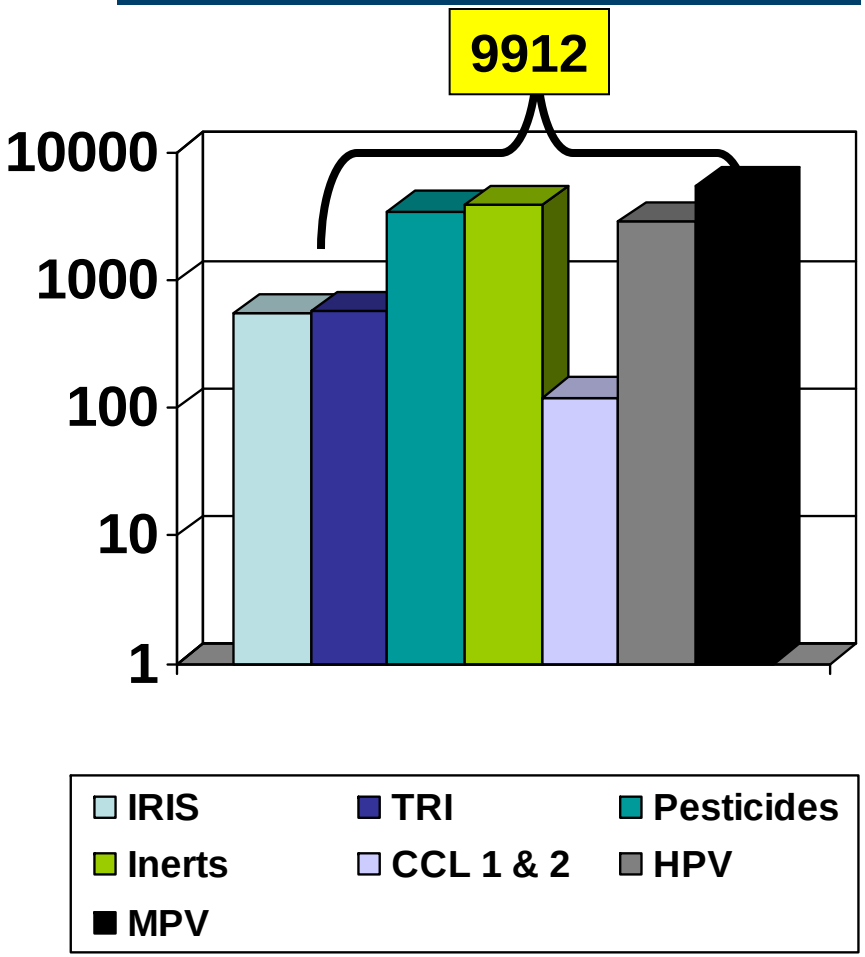
National Center for Computational Toxicology

United States Environmental Protection Agency

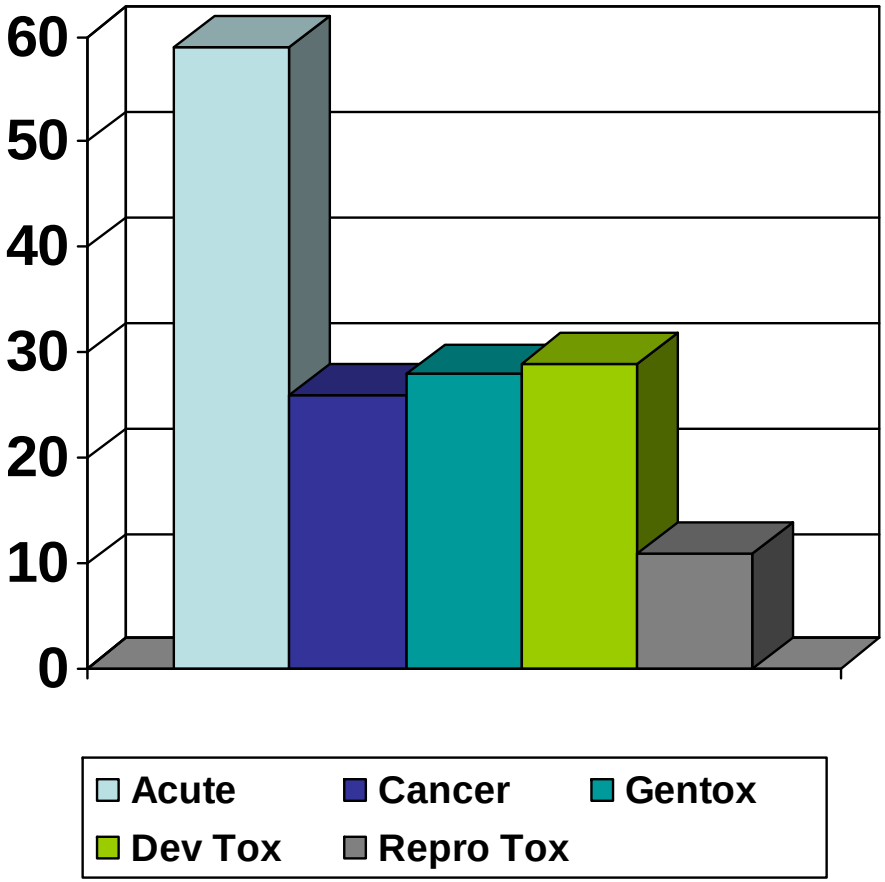
WHY?

EPA's Need for Prioritization

Too Many Chemicals



Too Little Data (%)



Judson, et al *EHP* (2009)

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There is a compelling need to develop approaches that will enable the screening and prioritization of large numbers of chemicals.

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WHAT?

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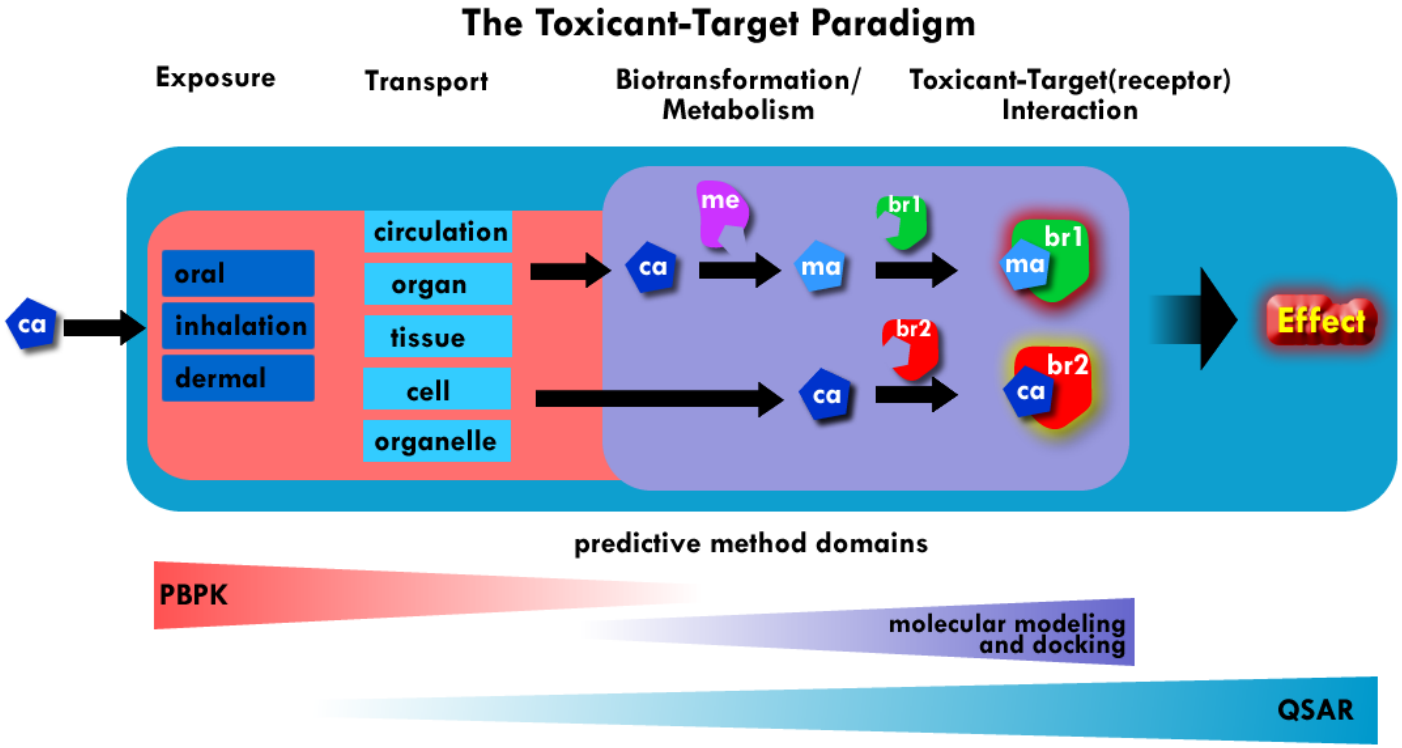
Knowledge of Mechanism of Toxicity Provides a Rational Basis for Extrapolation.



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Target-Toxicant Paradigm

- **The differential step in many mechanisms of toxicity may be generalized as the interaction between a small molecule (a toxicant) and one or more macromolecular targets.**

- **Targets could include genetic material, receptors, transport molecules, enzymes and others.**

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Target-Toxicant Paradigm

- **The difference in activity observed between chemicals acting through the same biological mode of action may then be understood as differences between their interactions with putative macromolecular targets.**

- **It is similar to the problem of screening a chemical data base for novel pharmaceutical agents**

- **Tools developed for that purpose may be applied**

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But there are important differences

- **Population of Chemicals**
  - **Specific types of ADME properties – Various ADME properties**
- **Strong Interactors - All Interactors**
- **Goal of the Screen is Different**
  - **Increase Hit Rate – Minimize false negatives**

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How?

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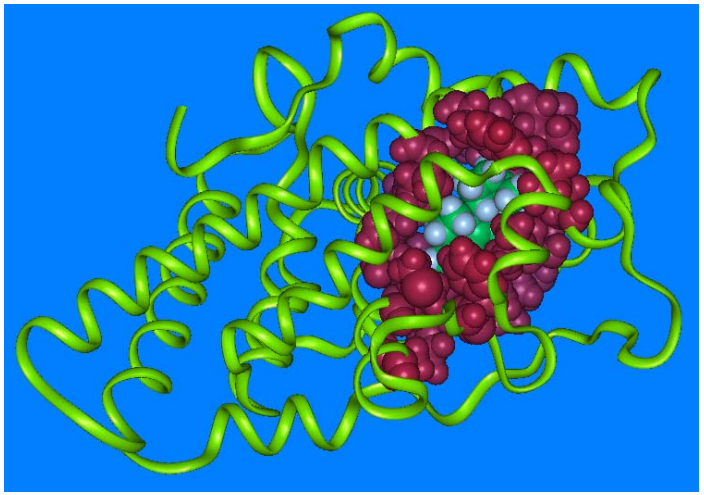
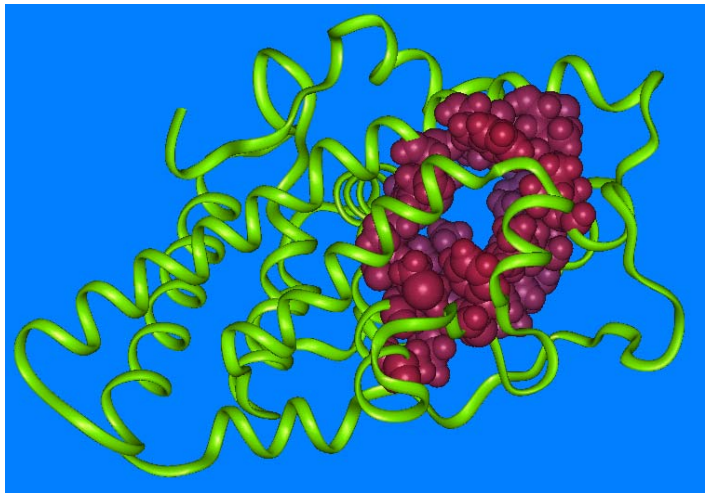
Computational Molecular Docking

Crystal structure from the PDB



1E3G Human Androgen Receptor Ligand Binding Domain with Ligand Metribolone (R1881)

Computationally created target



1E3G Human Androgen Receptor Ligand Binding Domain with Ligand removed computationally

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Docking Methods

- FRED
- eHiTS

FRED

Algorithm and Features

- Non-stochastic, systematic exploration of rotational and translational space
- Gaussian based scoring function
- Multilevel scoring and optimization
  - Rigid-body, torsional optimization
  - Rotors
- Specific scoring components
- Internal Pharmacophore
- Parallel implementation

eHits

- Exhaustive ----Divides molecule into fragments

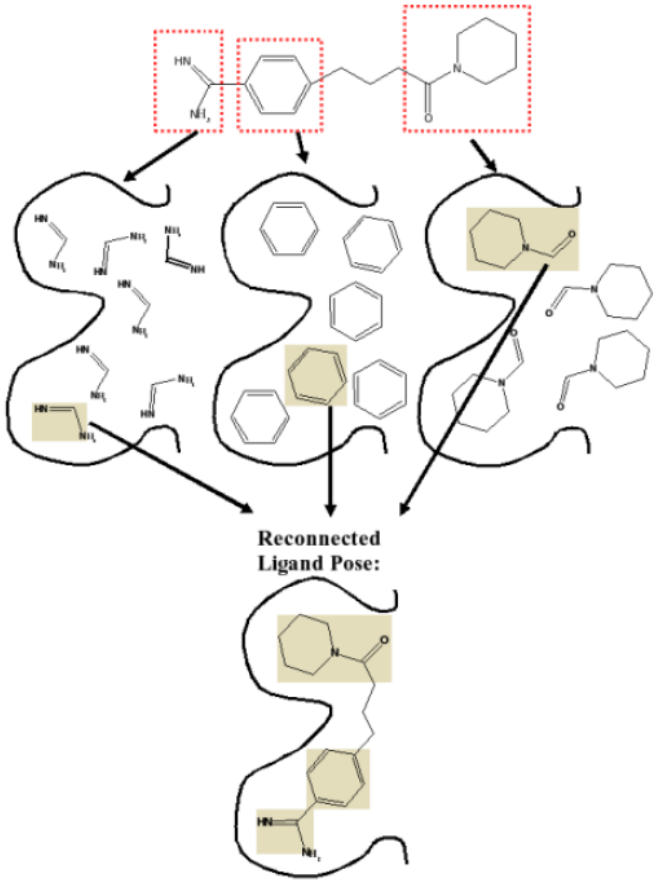
1. Ligands are divided into rigid fragments and connecting flexible chains

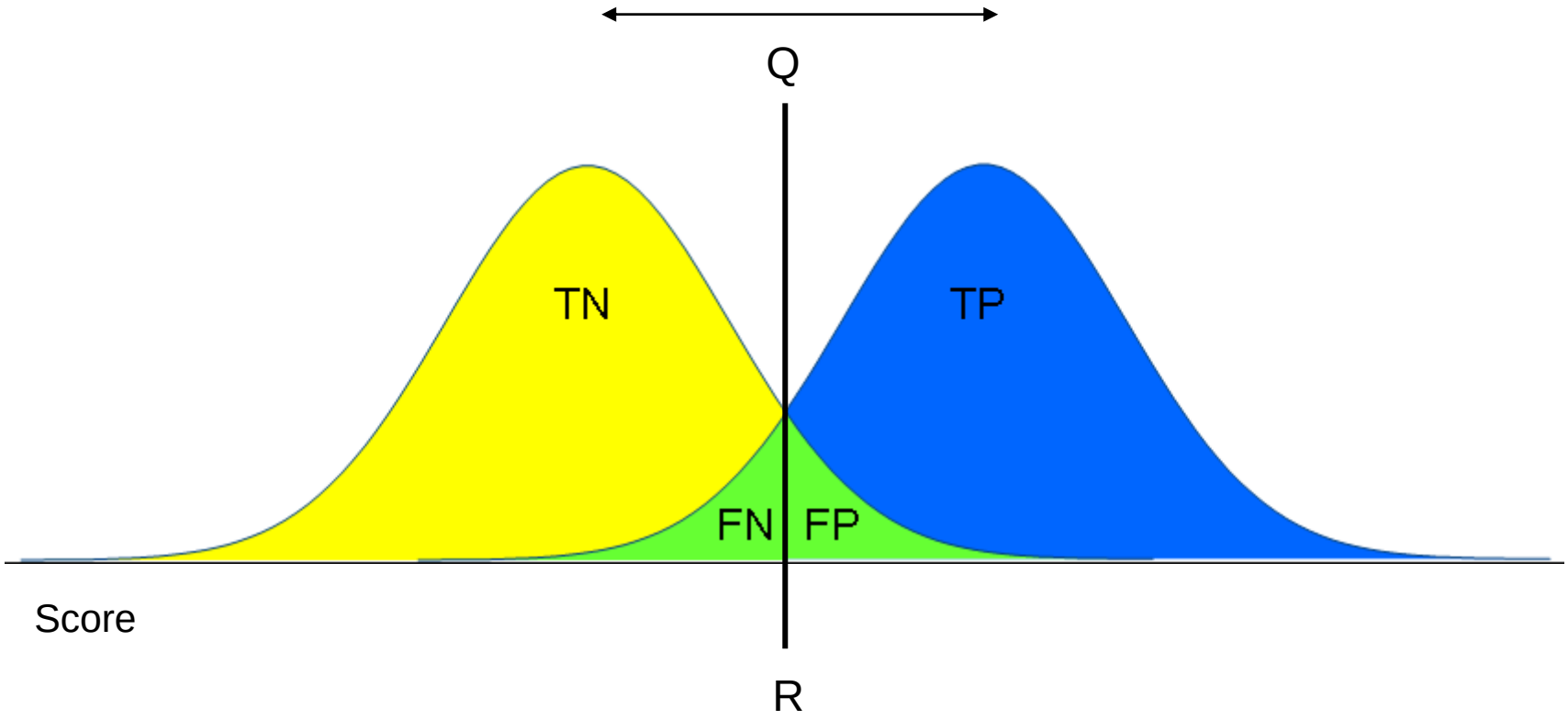
2. Rigid Dock: Each fragment is docked INDEPENDENTLY everywhere in the receptor

3. Pose Match: A fast graph matching algorithm finds all matching solutions to reconstruct the original molecule

4. Local Energy Optimization: structure is optimized within the receptor

5. Ranking: structures are ranked based on scoring function





	Experimental +	Experimental -
Predicted +	TP	FP
Predicted -	FN	TN

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Results!

An Experimental Data Set

Recently the data for the binding of a set of 281 chemicals to the rat estrogen receptor has been developed by EPA scientists.

Of these only 15 were found to be active.

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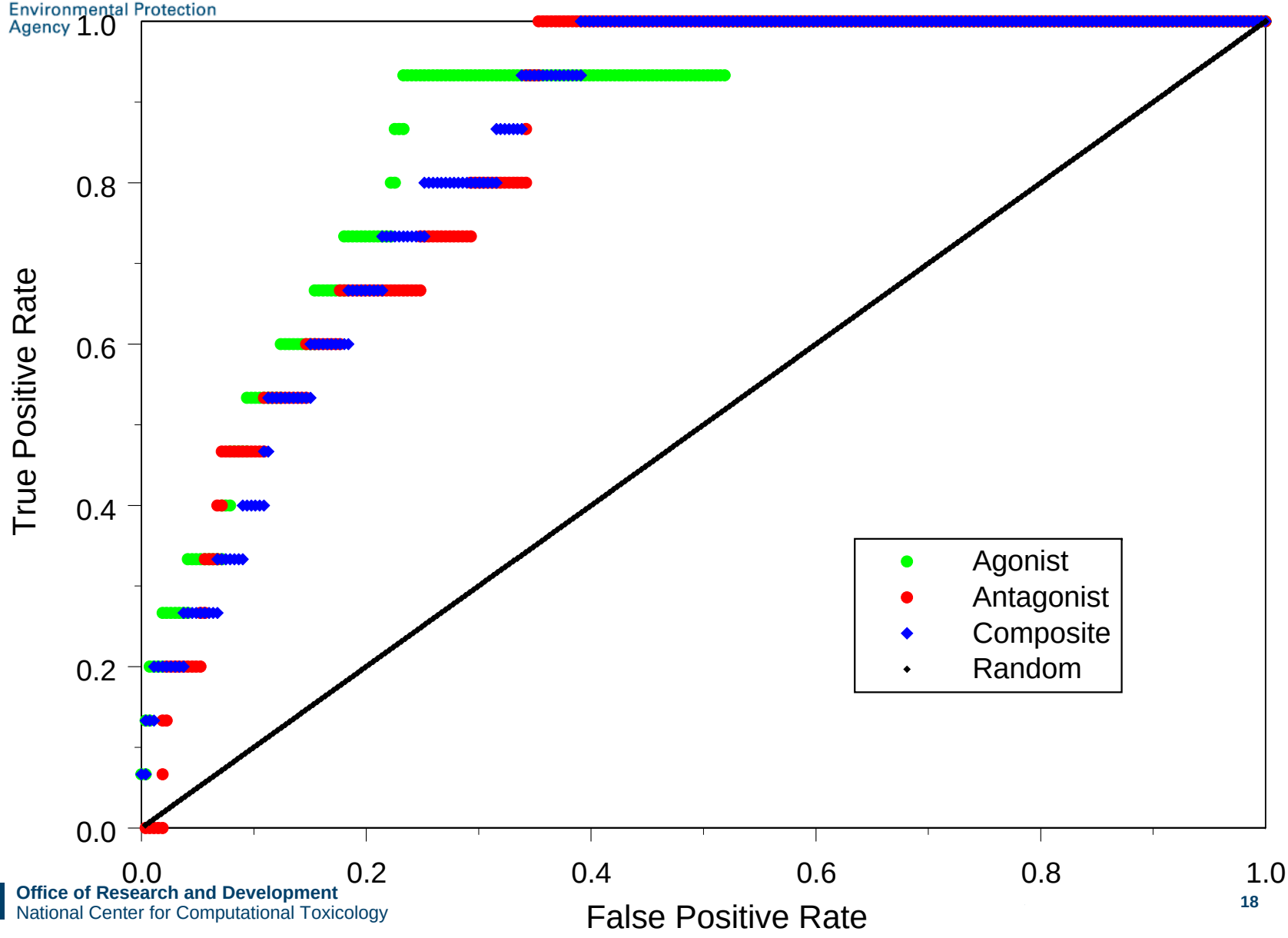
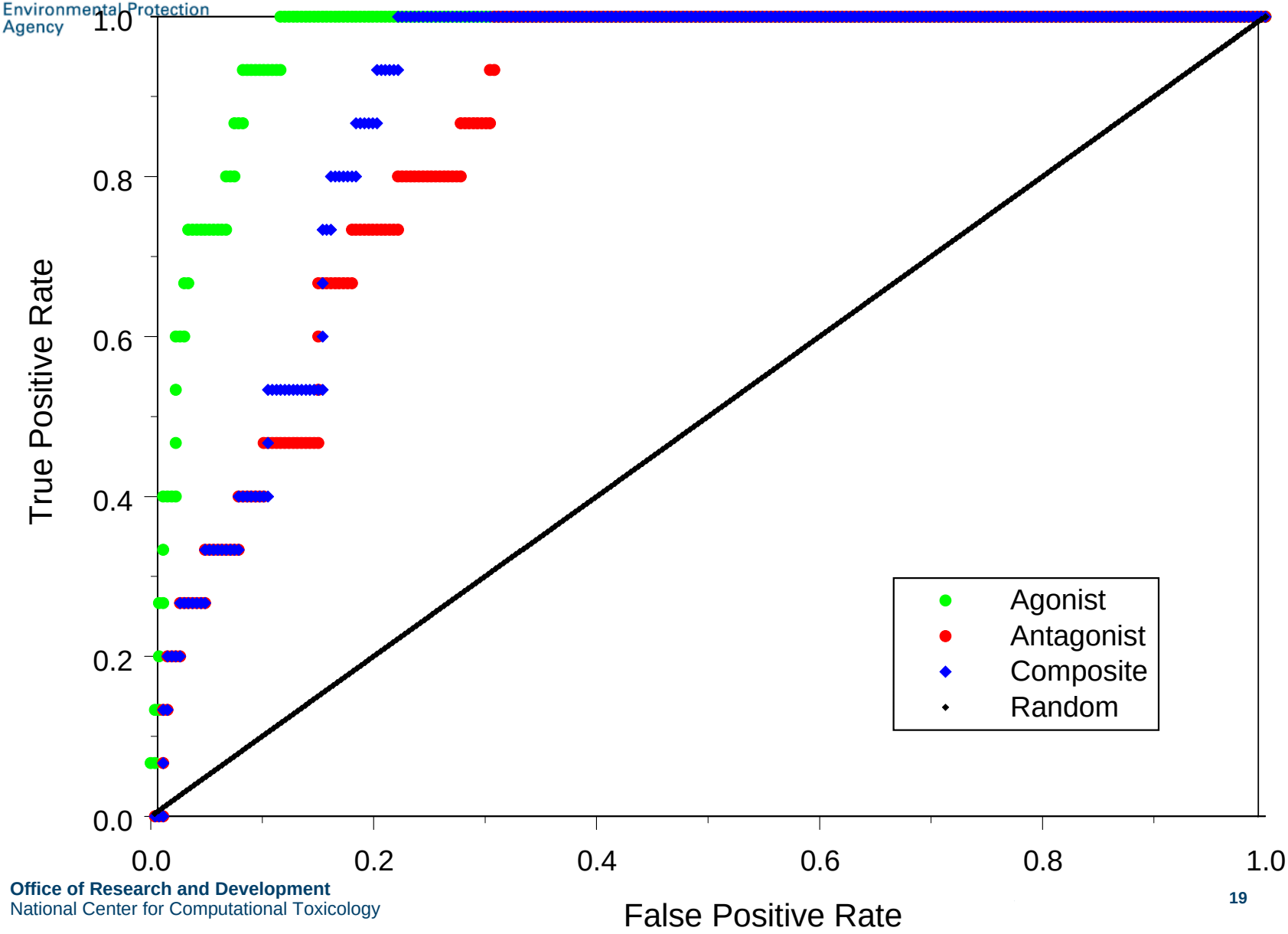
Receptors

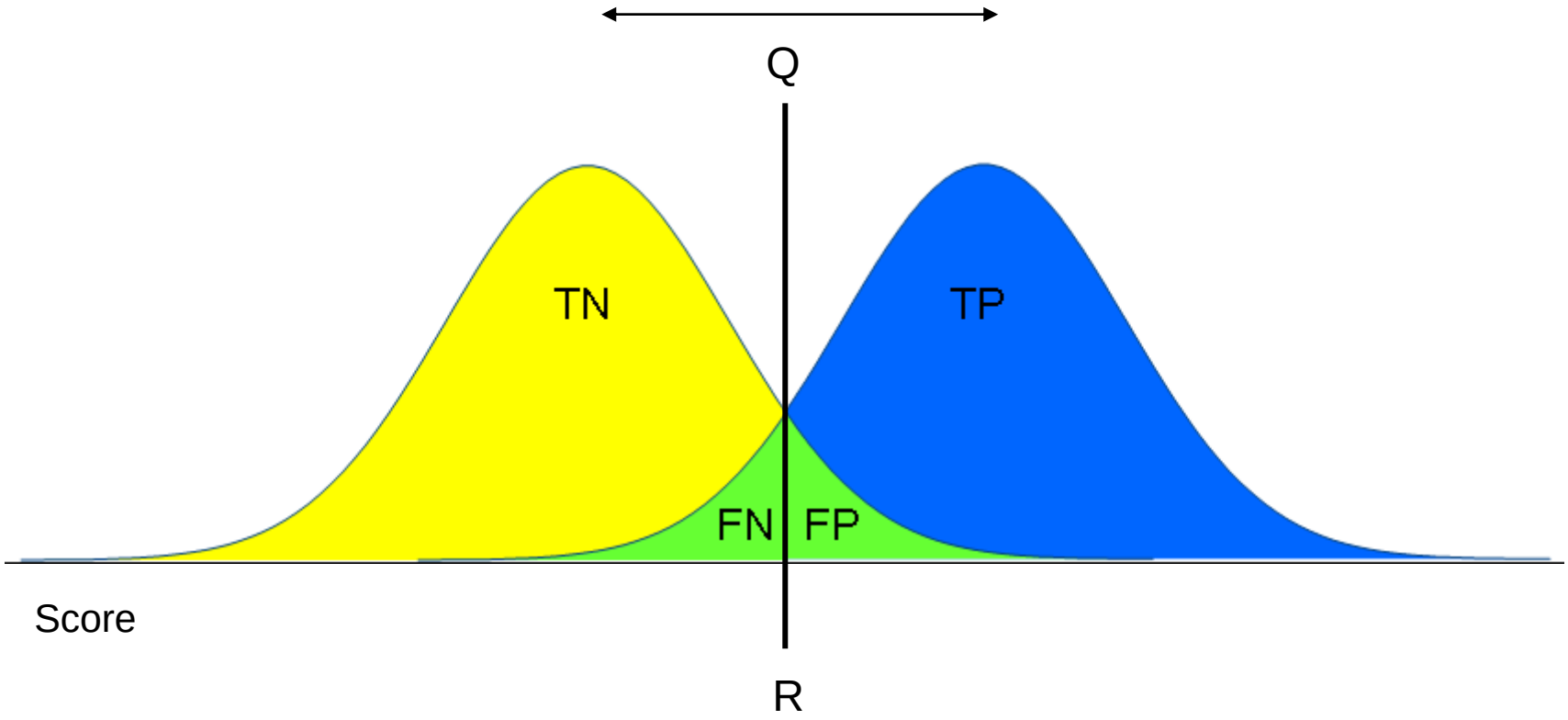
- Different Modes of Binding
  - Agonist Antagonist
- Different Proteins in the Same Tissue Prep
  - Alpha Beta
- Different Species
  - More human data
- Local Protein Flexibility
  - There are many estrogen receptor crystal structures with different ligands

Results with FRED no Constraints



Results with eHiTS no Constraints





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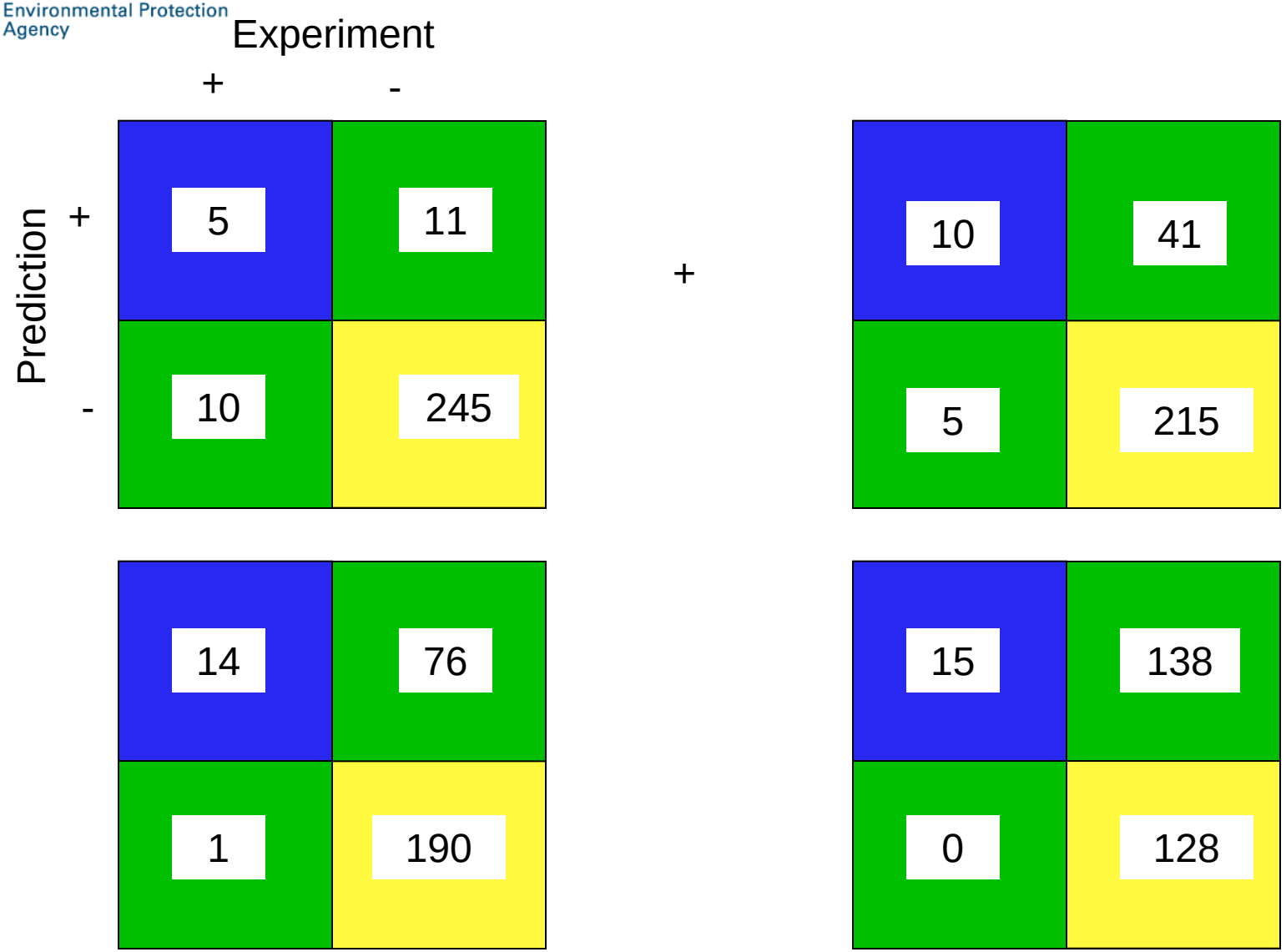

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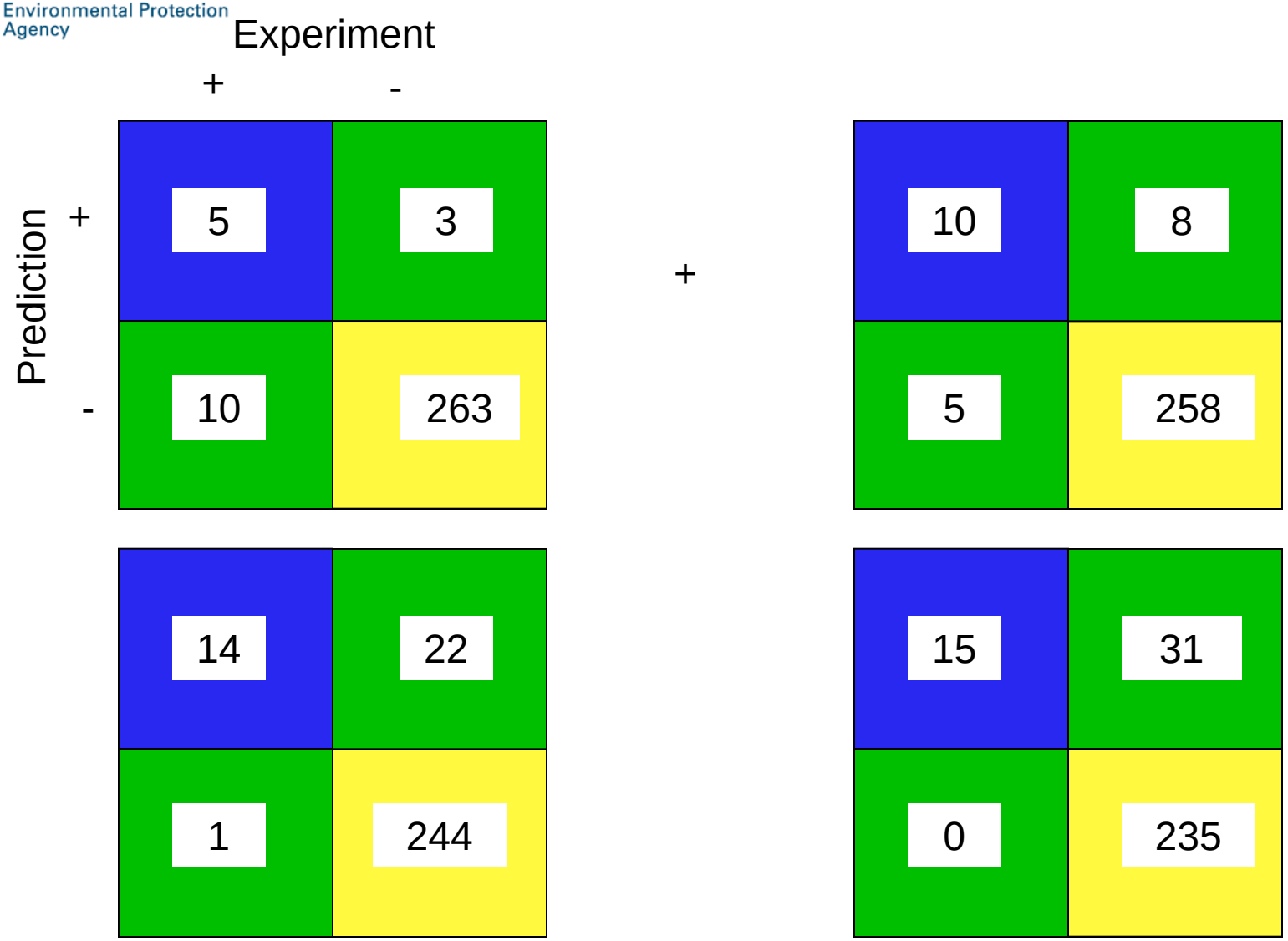
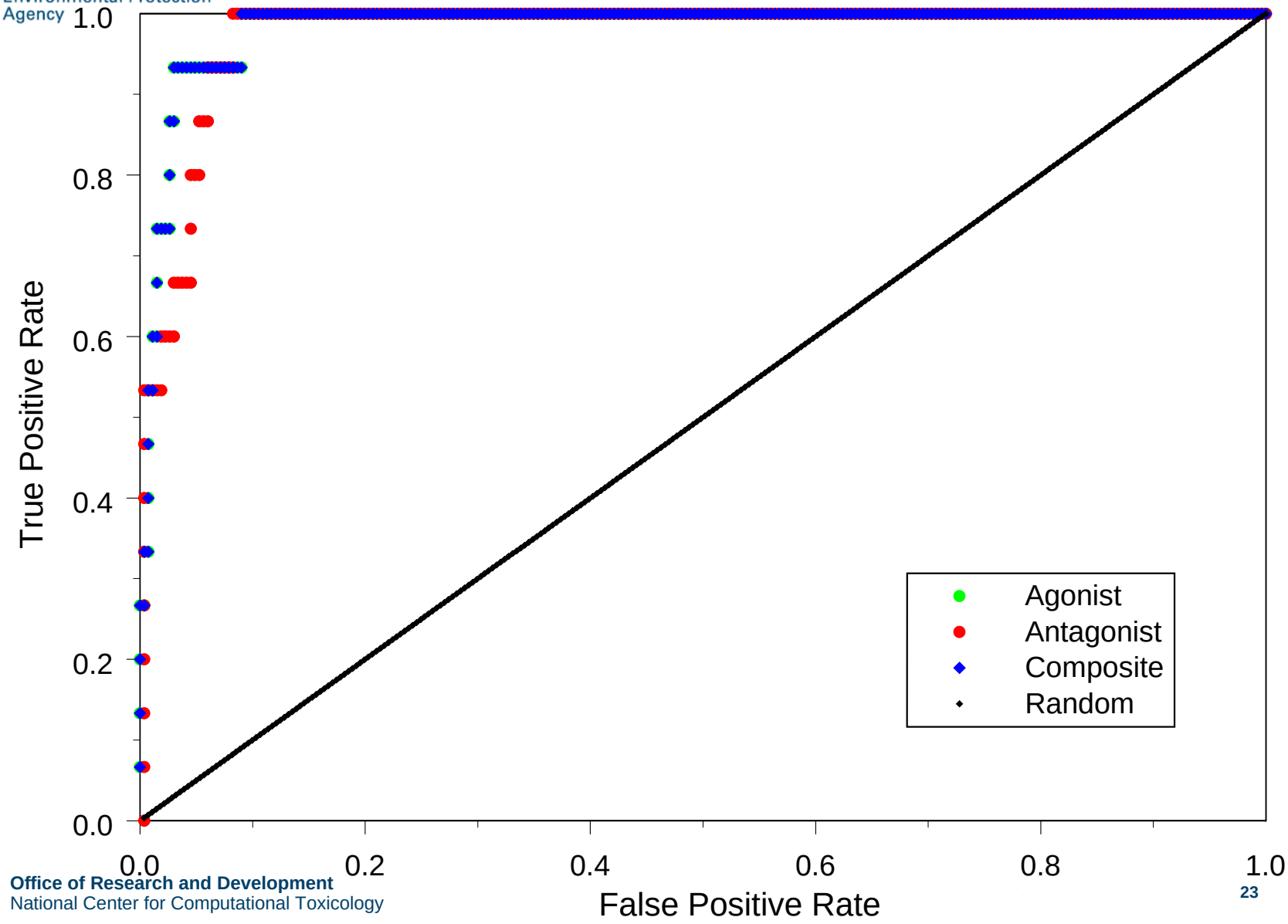
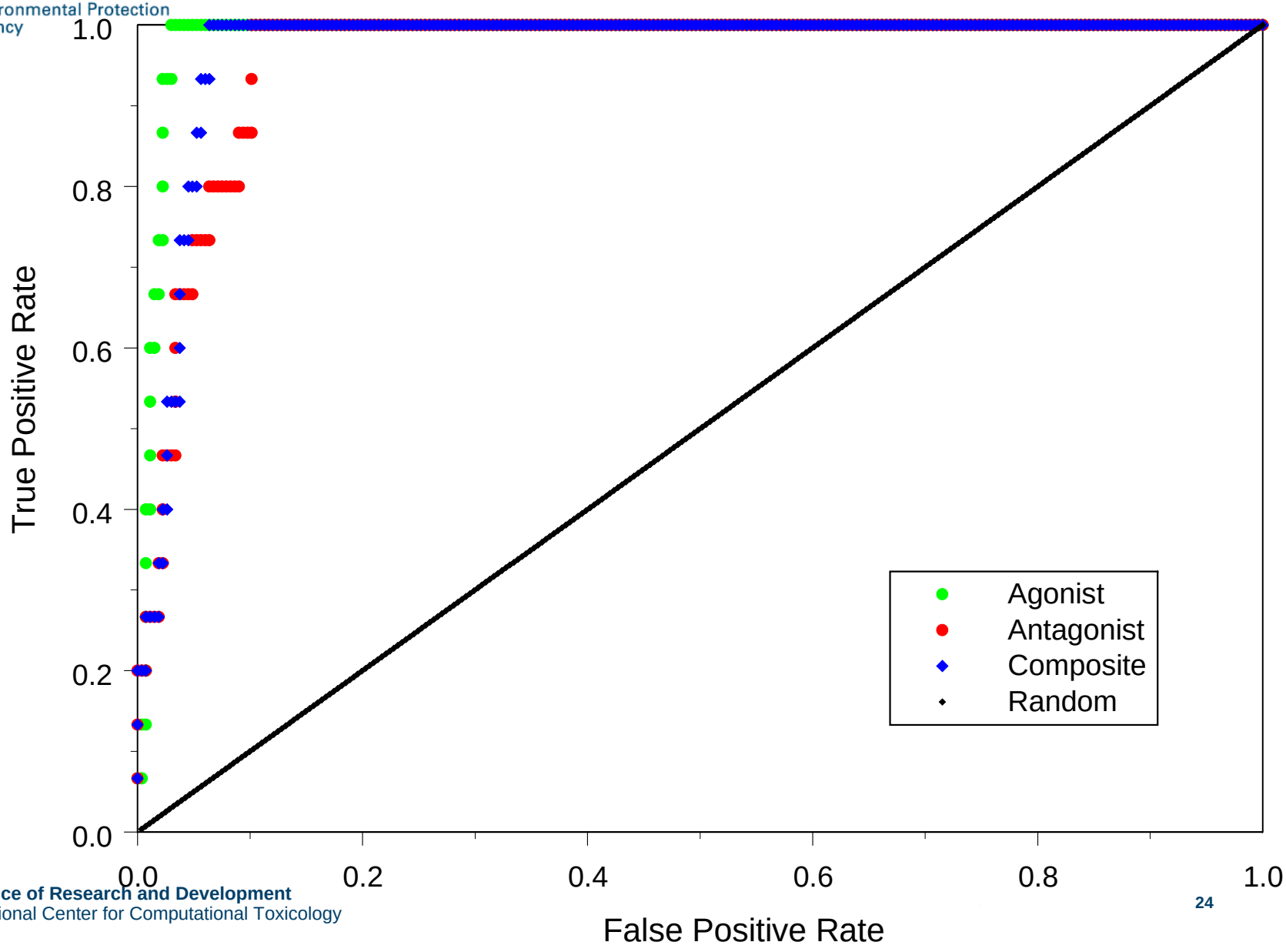


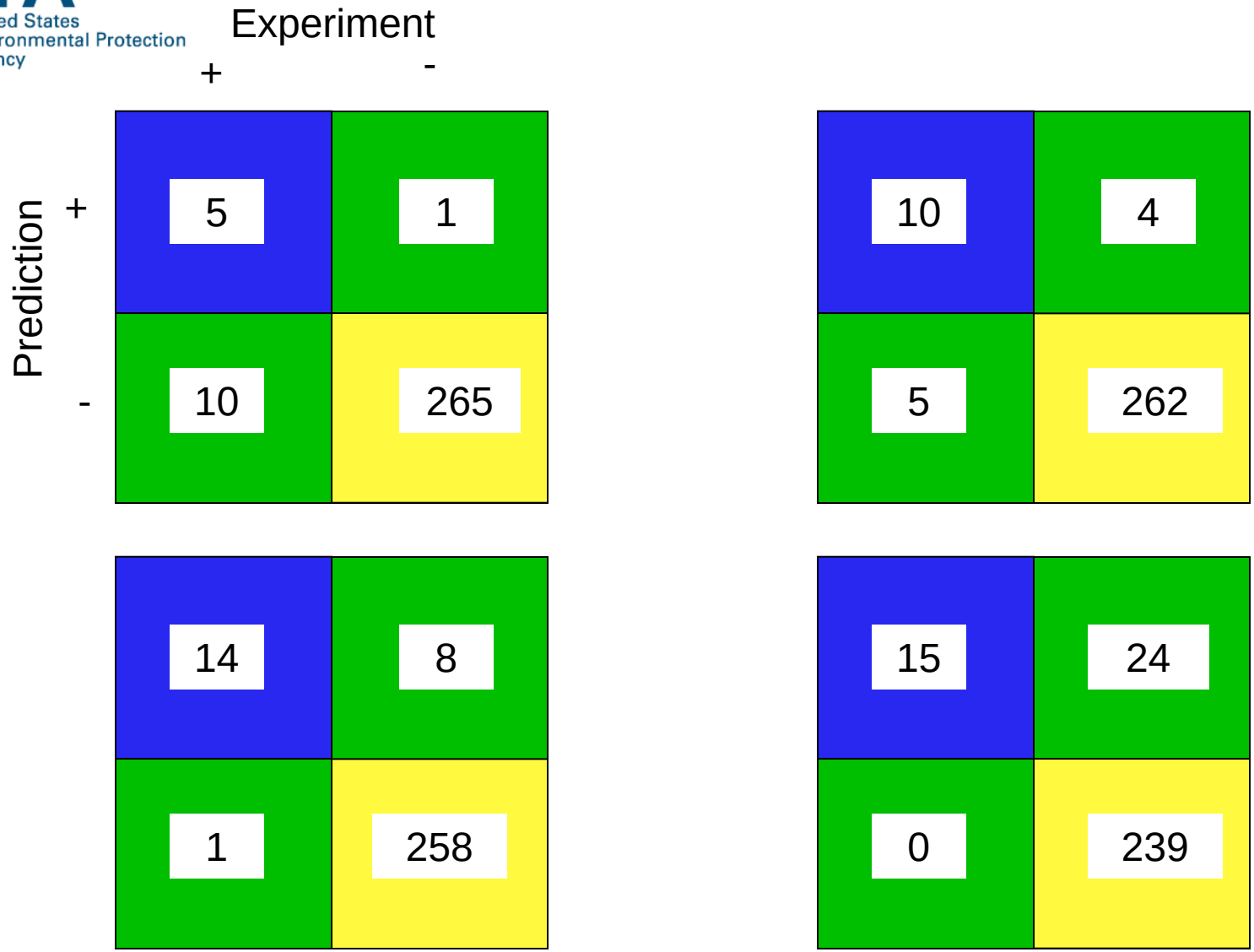
Results with FRED 2 Constraints



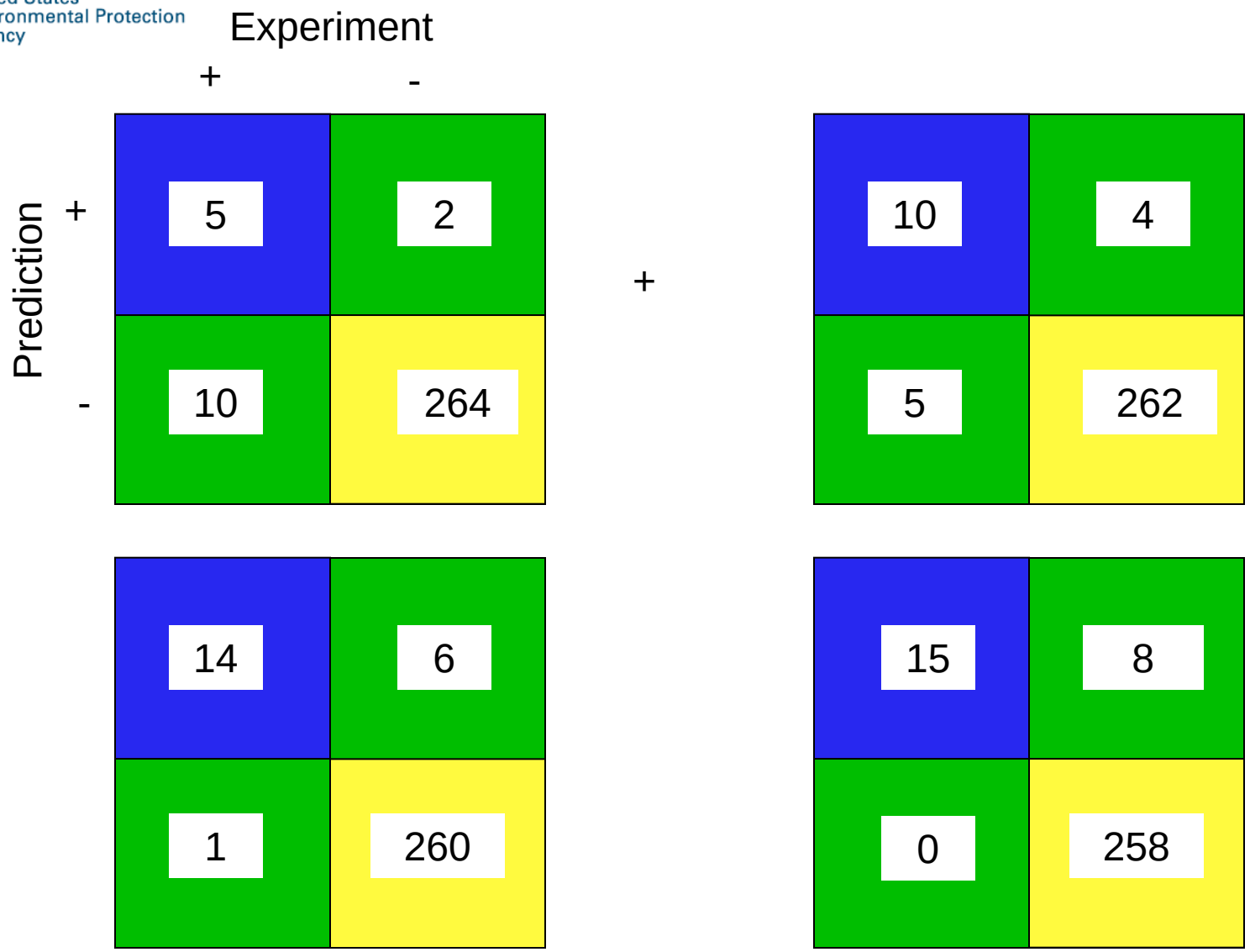
Results with eHiTS 2 Constraints



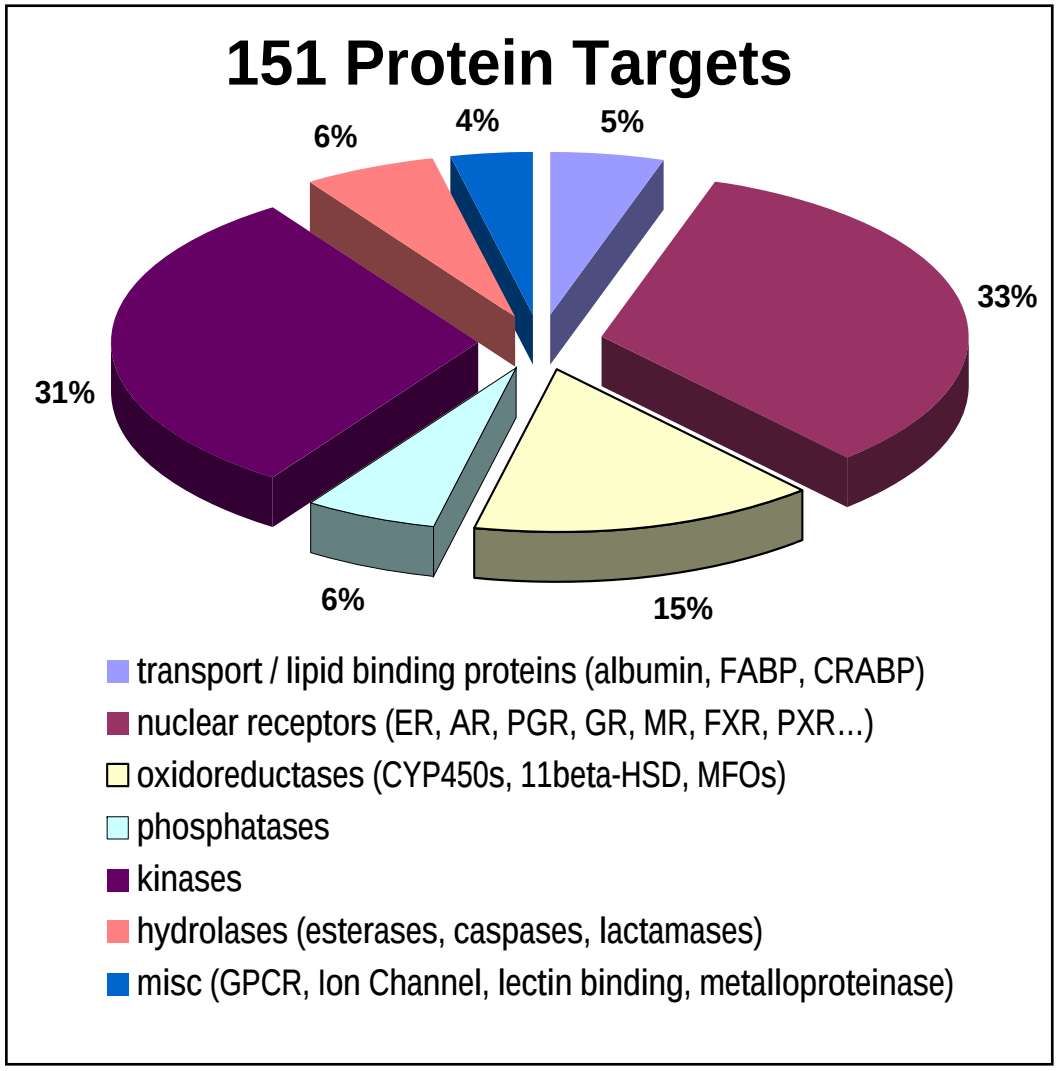
Results with FRED 2 Constraints



Results with eHiTS 2 Constraints



As this Approach Continues



Contributors and Acknowledgement

NHEERL/EPA
Susan Laws

Lockheed-Martin
Tom Transue

NCSU
Melissa Pasquinelli

This work was reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy.