Addressing Toxicity Risk when Designing and Selecting Compounds in Early Drug Discovery

Lhasa Limited vICGM, 18th June 2014

- Scott McDonald – Lhasa Limited
- Matthew Segall – Optibrium

Overview

- Lhasa and Derek
- Optibrium and StarDrop
- Derek Nexus and StarDrop

Who are Lhasa Limited

- Not-for-profit organisation
- Registered educational charity
- Controlled by our members
- Expertise in developing *in silico* prediction and database systems

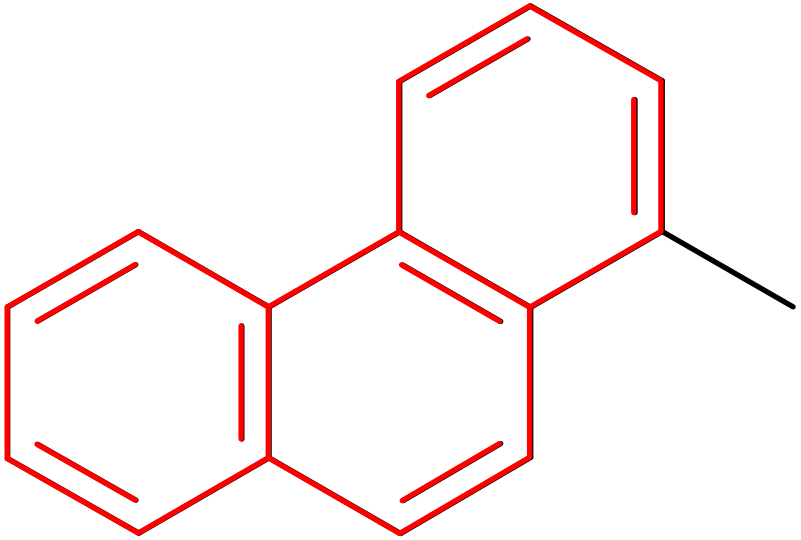
Derek Nexus

- Knowledge based expert system
- Enables the evaluation of the potential toxicity of chemicals
- Decision support tool
  - Accuracy
  - Transparency
  - Supporting data
- Covers a broad range of toxicity endpoints

Derek Nexus

Alert 754 – Mutagenicity in vitro

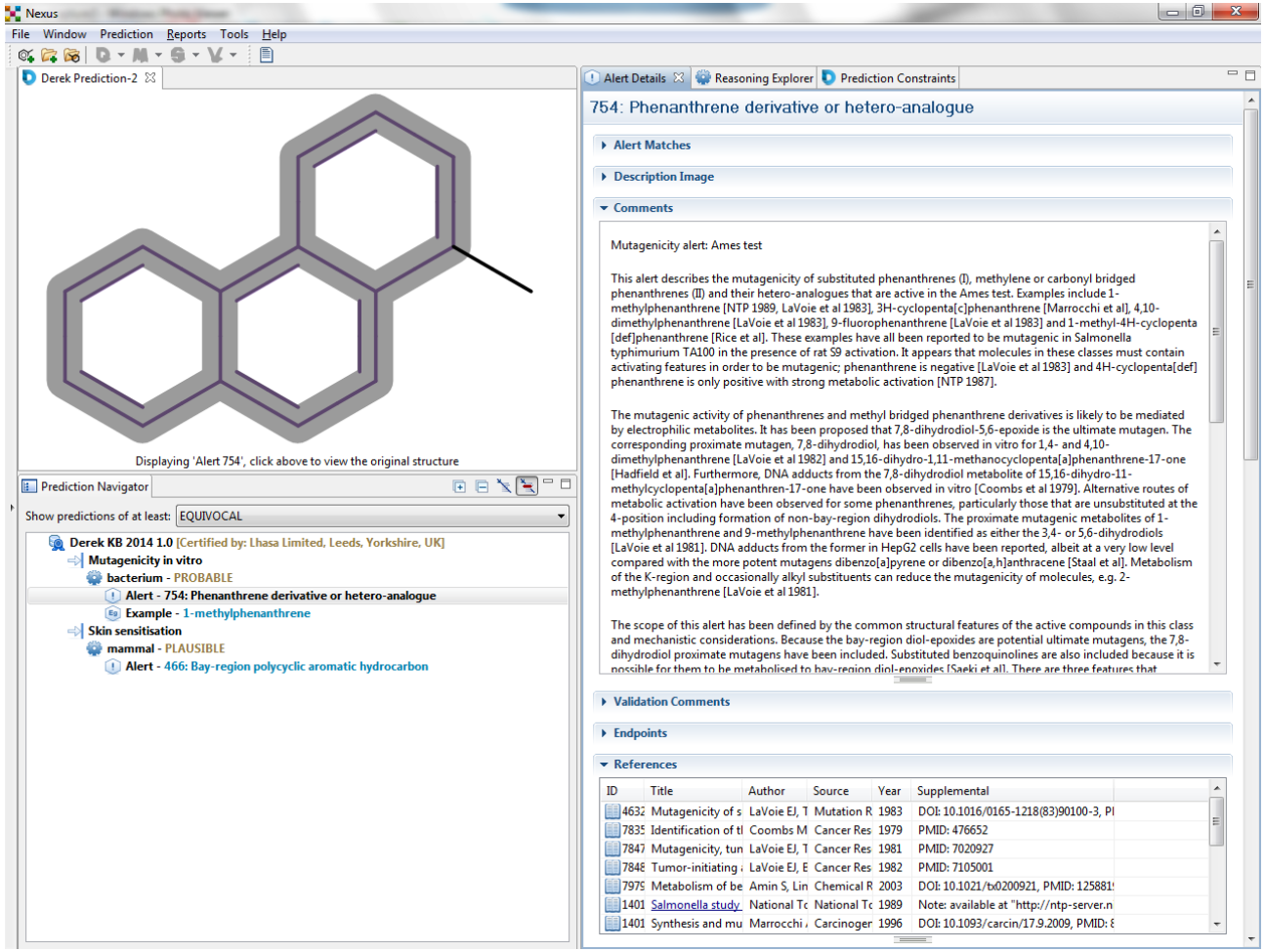
Bacterium - PROBABLE



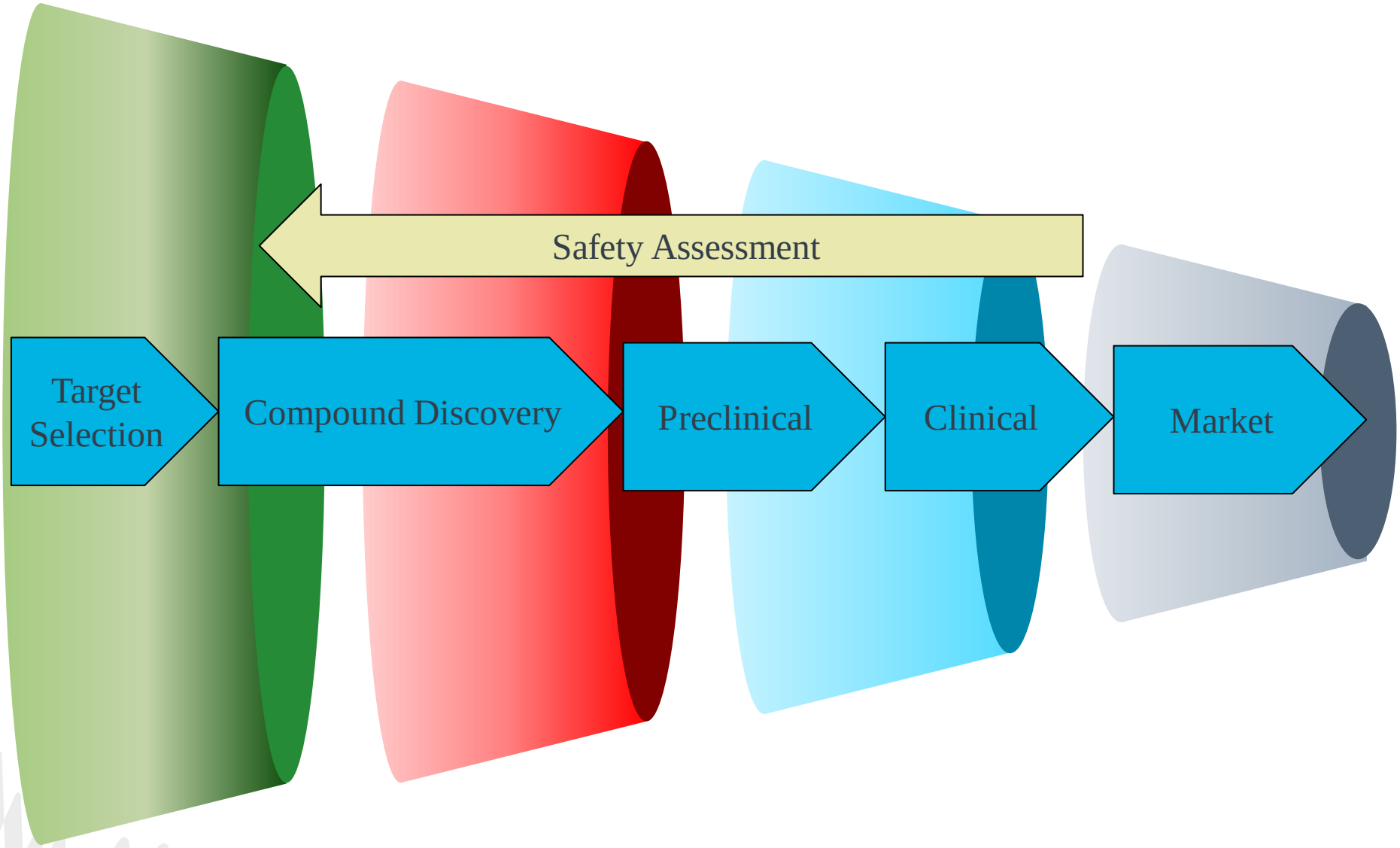
- Knowledge base search for matching structural alerts
- Application of rules – level of likelihood
- Supporting information provided

Levels of Likelihood

- Certain
  - There is proof that the proposition is true
- Probable
  - At least one strong argument that the proposition is true and no arguments against it
- Plausible
  - The weight of evidence supports the proposition
- Equivocal
  - An equal weight of evidence for and against the proposition
- Doubted, Improbable, Impossible, Open, Contradicted


Nexus
File Window Prediction Reports Tools Help
Derek Prediction-2
Displaying 'Alert 754', click above to view the original structure
Prediction Navigator
Show predictions of at least: EQUIVOCAL
Derek KB 2014 1.0 [Certified by: Lhasa Limited, Leeds, Yorkshire, UK]
Mutagenicity in vitro
bacterium - PROBABLE
Alert - 754: Phenanthrene derivative or hetero-analogue
Example - 1-methylphenanthrene
Skin sensitisation
mammal - PLAUSIBLE
Alert - 466: Bay-region polycyclic aromatic hydrocarbon
Alert Details
Reasoning Explorer
Prediction Constraints
754: Phenanthrene derivative or hetero-analogue
Alert Matches
Description Image
Comments
Mutagenicity alert: Ames test
This alert describes the mutagenicity of substituted phenanthrenes (I), methylene or carbonyl bridged phenanthrenes (II) and their hetero-analogues that are active in the Ames test. Examples include 1-methylphenanthrene [NTP 1989, LaVoie et al 1983], 3H-cyclopenta[c]phenanthrene [Marrocchi et al], 4,10-dimethylphenanthrene [LaVoie et al 1983], 9-fluorophenanthrene [LaVoie et al 1983] and 1-methyl-4H-cyclopenta[def]phenanthrene [Rice et al]. These examples have all been reported to be mutagenic in Salmonella typhimurium TA100 in the presence of rat S9 activation. It appears that molecules in these classes must contain activating features in order to be mutagenic; phenanthrene is negative [LaVoie et al 1983] and 4H-cyclopenta[def]phenanthrene is only positive with strong metabolic activation [NTP 1987].
The mutagenic activity of phenanthrenes and methyl bridged phenanthrene derivatives is likely to be mediated by electrophilic metabolites. It has been proposed that 7,8-dihydrodiol-5,6-epoxide is the ultimate mutagen. The corresponding proximate mutagen, 7,8-dihydrodiol, has been observed in vitro for 1,4- and 4,10-dimethylphenanthrene [LaVoie et al 1982] and 15,16-dihydro-1,11-methanocyclopenta[a]phenanthrene-17-one [Hadfield et al]. Furthermore, DNA adducts from the 7,8-dihydrodiol metabolite of 15,16-dihydro-11-methylcyclopenta[a]phenanthren-17-one have been observed in vitro [Coombs et al 1979]. Alternative routes of metabolic activation have been observed for some phenanthrenes, particularly those that are unsubstituted at the 4-position including formation of non-bay-region dihydrodiols. The proximate mutagenic metabolites of 1-methylphenanthrene and 9-methylphenanthrene have been identified as either the 3,4- or 5,6-dihydrodiols [LaVoie et al 1981]. DNA adducts from the former in HepG2 cells have been reported, albeit at a very low level compared with the more potent mutagens dibenzo[a]pyrene or dibenzo[a,h]anthracene [Staal et al]. Metabolism of the K-region and occasionally alkyl substituents can reduce the mutagenicity of molecules, e.g. 2-methylphenanthrene [LaVoie et al 1981].
The scope of this alert has been defined by the common structural features of the active compounds in this class and mechanistic considerations. Because the bay-region diol-epoxides are potential ultimate mutagens, the 7,8-dihydrodiol proximate mutagens have been included. Substituted benzoquinolines are also included because it is
Validation Comments
Endpoints
References
ID Title Author Source Year Supplemental
4632 Mutagenicity of s LaVoie EJ, T Mutation R 1983 DOI: 10.1016/0165-1218(83)90100-3, PI
7835 Identification of tl Coombs M Cancer Res 1979 PMID: 476652
7847 Mutagenicity, tun LaVoie EJ, T Cancer Res 1981 PMID: 7020927
7848 Tumor-initiating a LaVoie EJ, E Cancer Res 1982 PMID: 7105001
7975 Metabolism of be Amin S, Lin Chemical R 2003 DOI: 10.1021/tx0200921, PMID: 125881
1401 Salmonella study National Tc National Tc 1989 Note: available at "http://ntp-server.n
1401 Synthesis and mu Marrocchi a Carcinoger 1996 DOI: 10.1093/carcin/17.9.2009, PMID:

Drug Discovery



Lhasa and Optibrium

- Collaboration commenced in 2013
- Development of the Derek Nexus Module for StarDrop
- Available as an optional module
- Facilitates the design of safe drugs in hit-to-lead and lead optimisation

optibrium

Addressing Toxicity Risk when Designing and Selecting Compounds in Early Drug Discovery

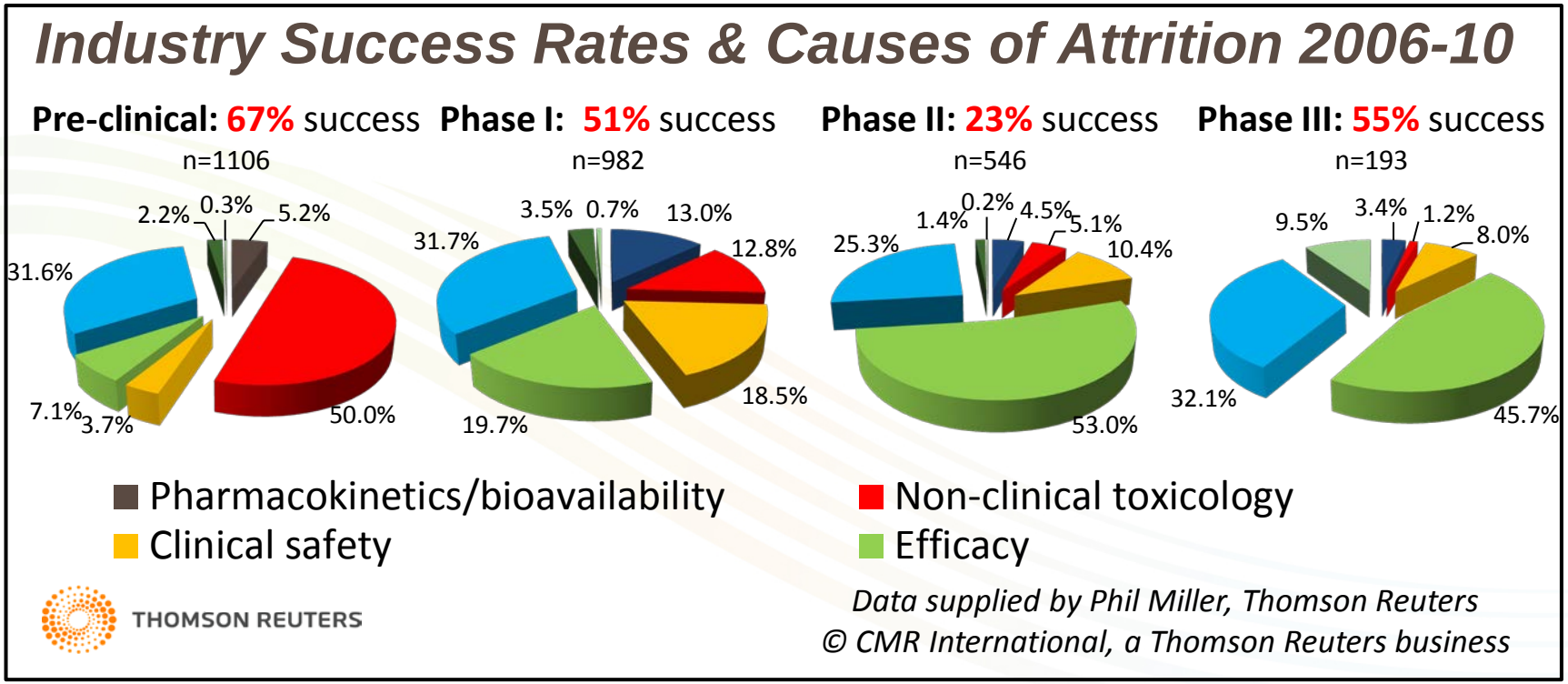
Lhasa Limited vICGM, 18th June 2014

Matthew Segall, Chris Barber

Overview

- Impact of toxicity in pharma. R&D
- Application of knowledge based prediction of toxicity
- Guiding compound selection and design
  - Multi-parameter optimisation
  - Glowing Molecule
- Example
  - Exploring a COX2 screening library
- Short overview of StarDrop and the Derek Nexus module
- Conclusions

Impact of Toxicity in Pharma R&D

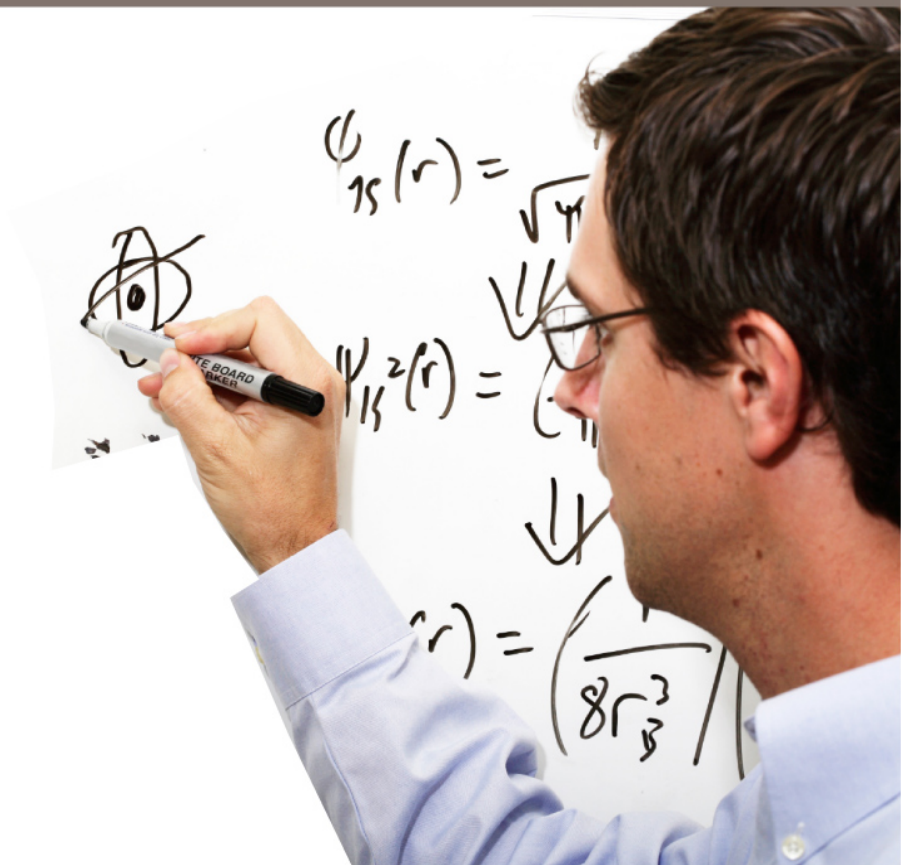


- 54% of pre-clinical failures due to tox/safety (18% of all candidates)
- 22% of all clinical candidates failed due to tox/safety
- 10.2% of approved drugs acquired black box warning, 2.9% withdrawn*

*Lasser, *et al.* (2002) *JAMA* 287, 2215-2220.

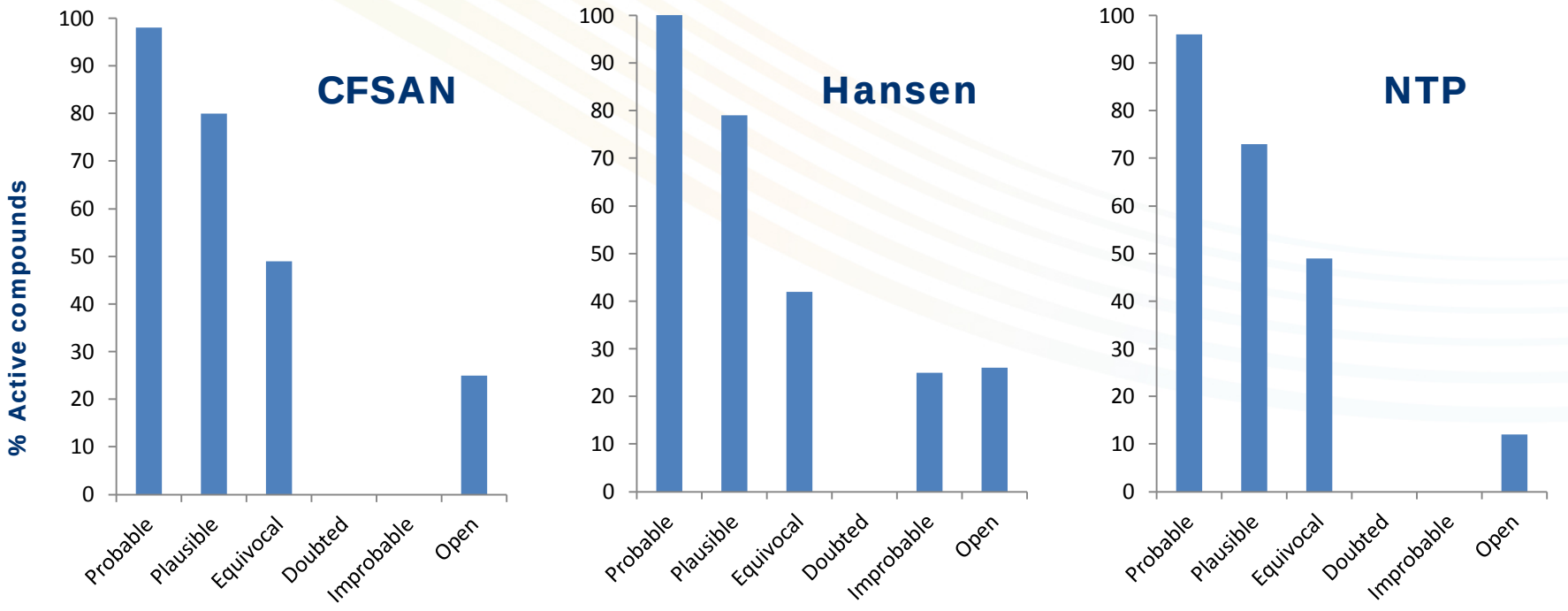
Application of Knowledge Based Prediction of Toxicity

optibrium



Relating confidence and accuracy

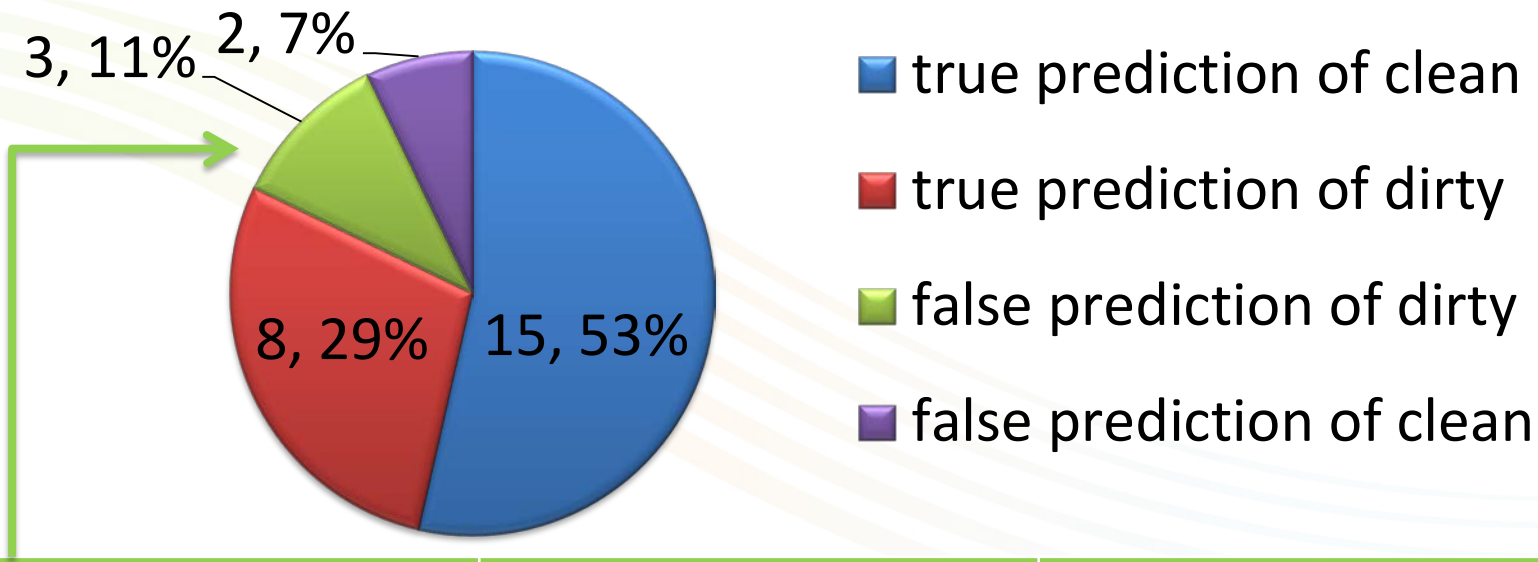
- Derek Nexus provides a level of confidence (likelihood) for each prediction
  - This correlates well with accuracy



Judson *et. al. Toxicology Research*, 2013, *2*, 70

How Well do Expert Systems Perform?

- CDER approved drugs 2012 (n=27)



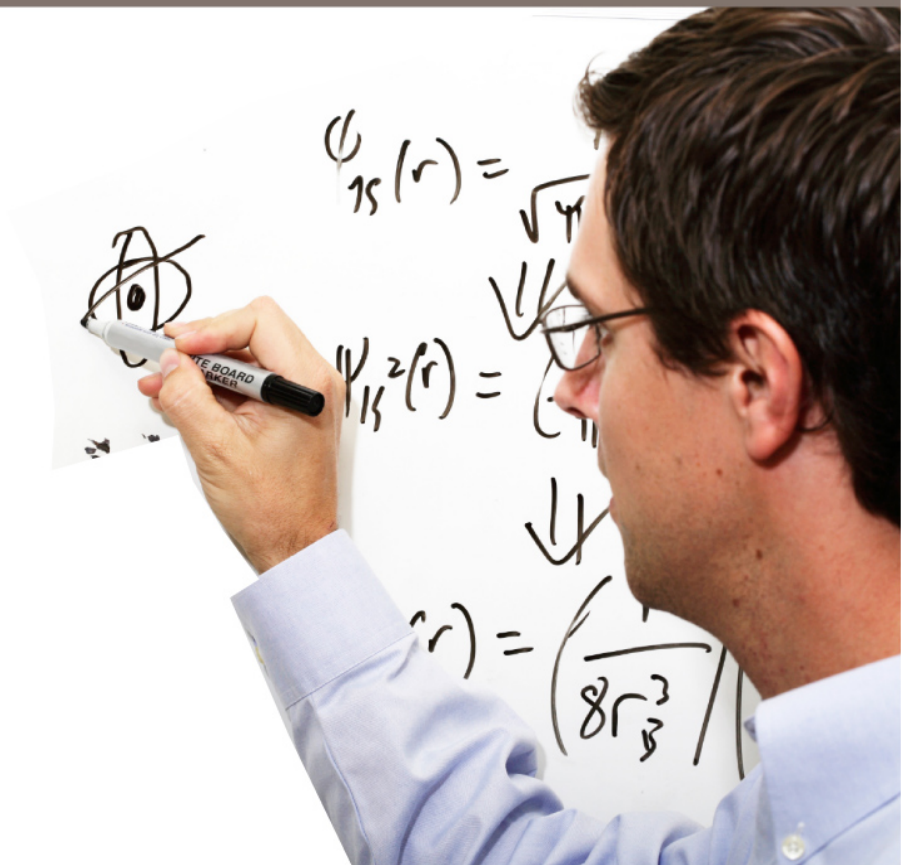
drug *indication*	**prediction**	**dosing**
Ingenol *actinic keratoses*	chromosomal damage	topical treatment (cytotoxic mechanism)
Aclidinium *COPD*	hepatotoxic	inhaled (0.4mg dose)
Linaclotide *IBS*	hepatotoxic	metabolised in GI tract

Important Caveats/Questions

- Predict toxicity hazard
  - Risk ≈ hazard + exposure
  - Risk also depends on dose, route of administration, therapeutic index...
- Knowledge-based prediction of toxicity widely used in preclinical development
  - Assessment of risk for regulatory submission
  - Design of experiments to support submissions
- Question: How can these predictions be applied effectively in early drug discovery?
  - We don't want to 'kill' potentially good compounds at an early stage due to uncertain predictions

Guiding Compound Design and Selection

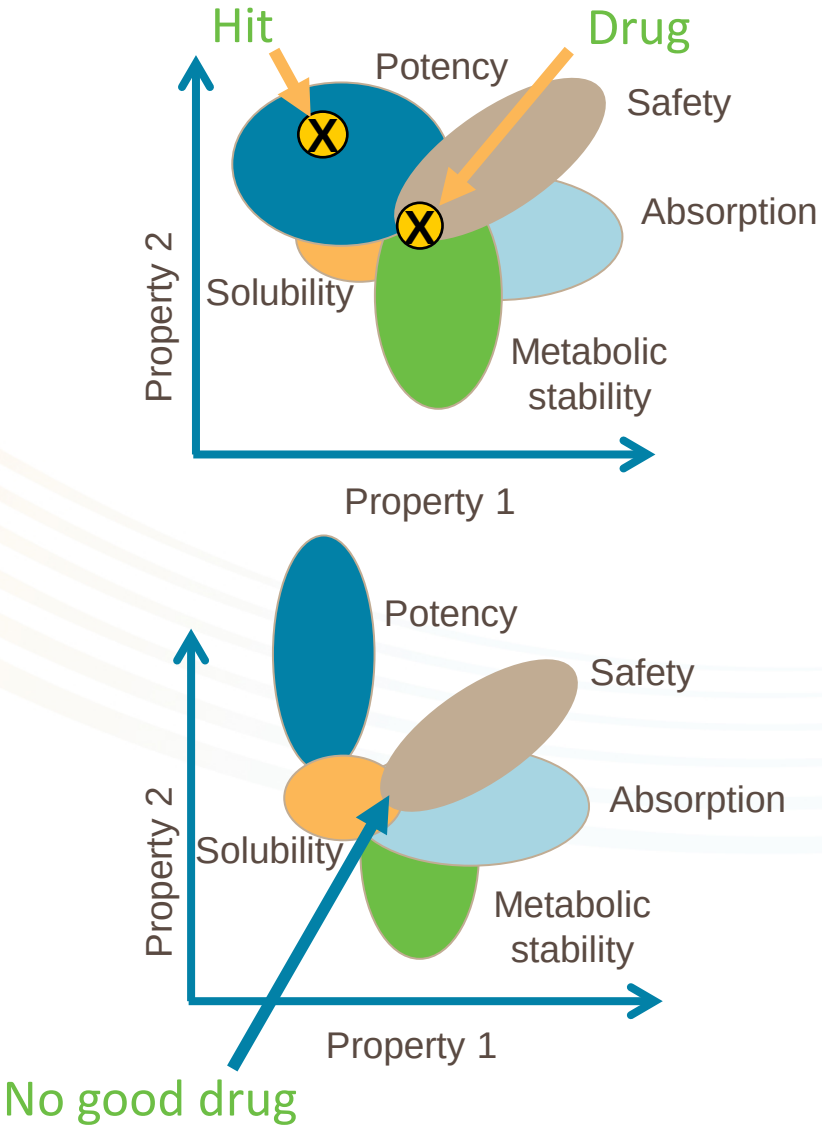
optibrium



The Objectives
Multi-parameter optimisation

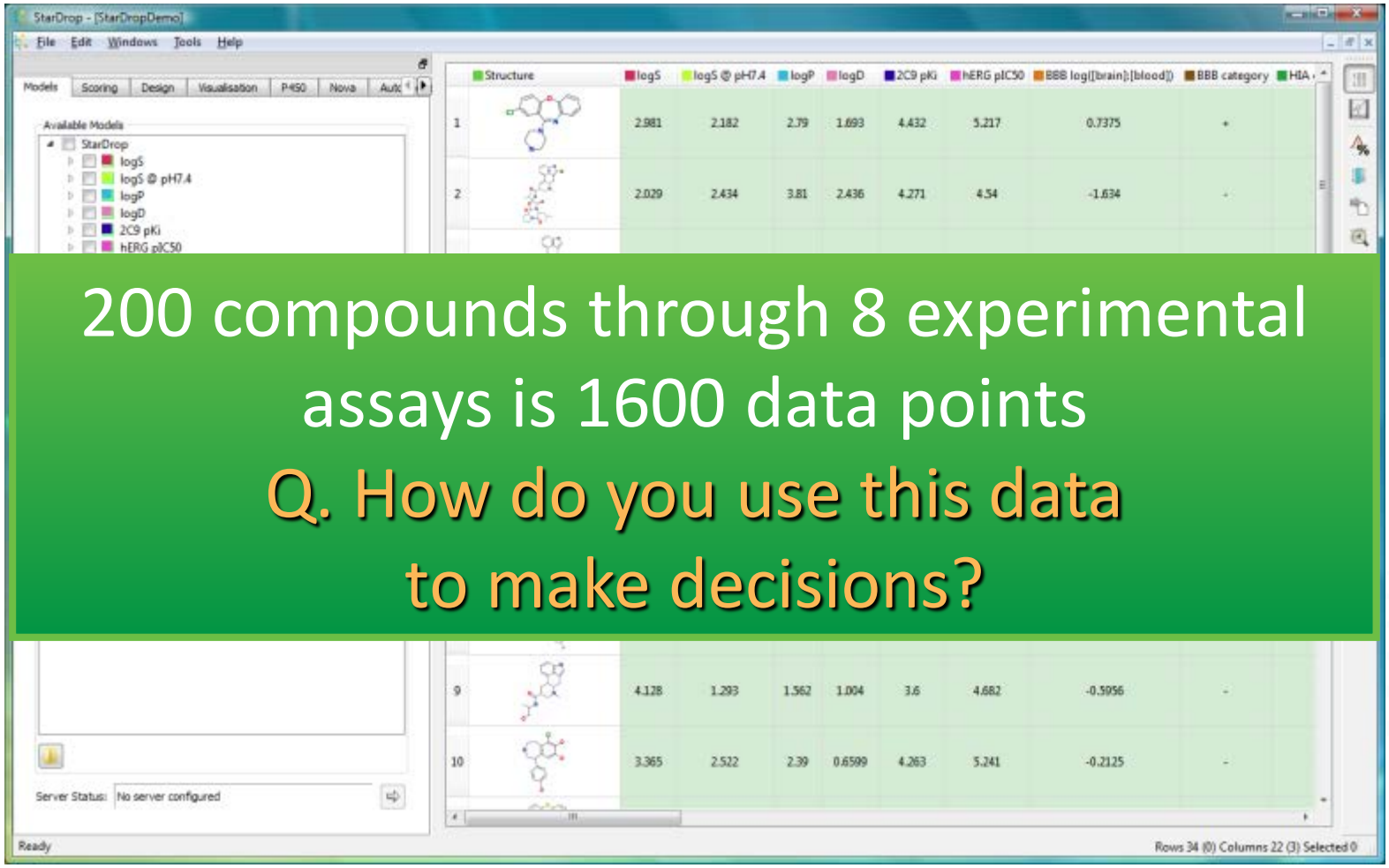
- Identify chemistries with an optimal **balance** of properties

- Quickly identify situations when such a balance is not possible
  - –Fail fast, fail cheap
  - –Only when **confident**



*M.D. Segall Curr. Pharm. Des. **18**(9) pp. 1292-1310 (2012)

The Challenge



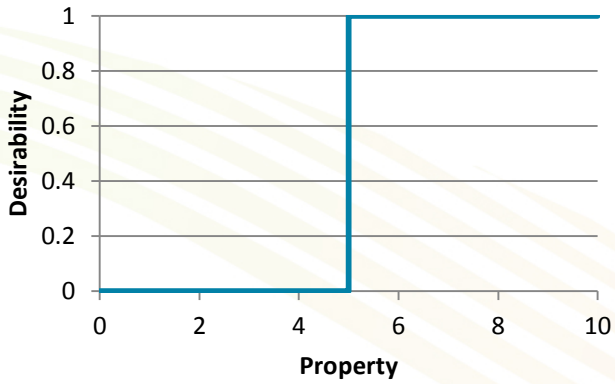
200 compounds through 8 experimental assays is 1600 data points

Q. How do you use this data to make decisions?

Approaches for MPO
Filtering?

Approaches for MPO
Desirability Functions*

- Relate property values to how ‘desirable’ the outcome

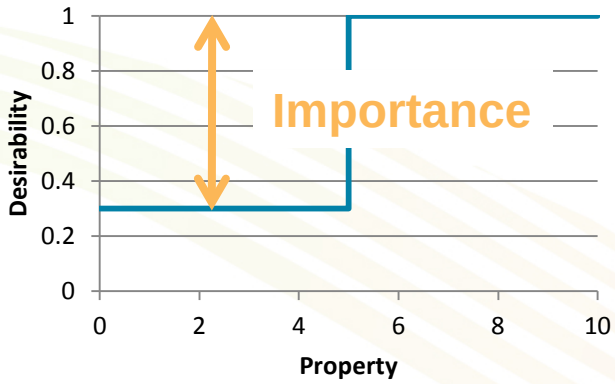


Simple filter: >5

* Harrington EC. (1965) Ind. Qual. Control. **21** p. 494

Approaches for MPO
Desirability Functions*

- Relate property values to how ‘desirable’ the outcome

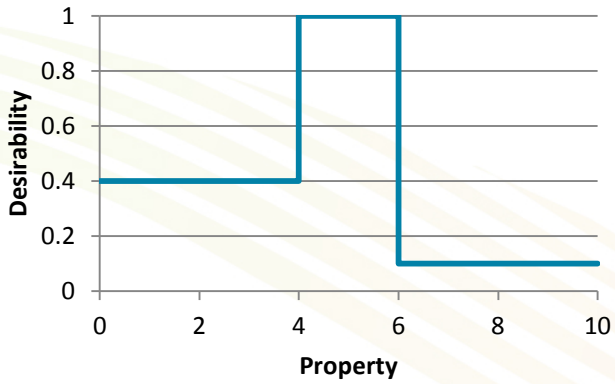


Desired value: >5

* Harrington EC. (1965) Ind. Qual. Control. **21** p. 494

Approaches for MPO
Desirability Functions*

- Relate property values to how ‘desirable’ the outcome

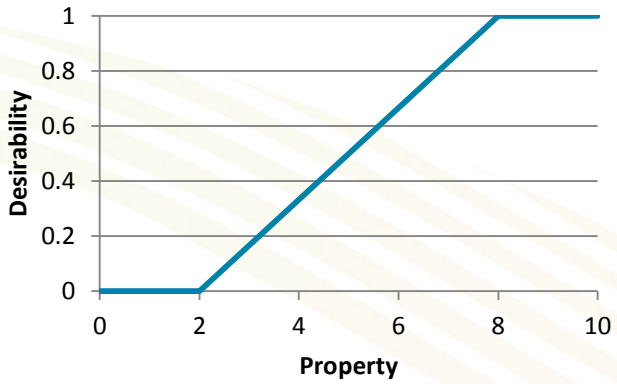


Rang: 4-6

* Harrington EC. (1965) Ind. Qual. Control. **21** p. 494

Approaches for MPO
Desirability Functions*

- Relate property values to how ‘desirable’ the outcome

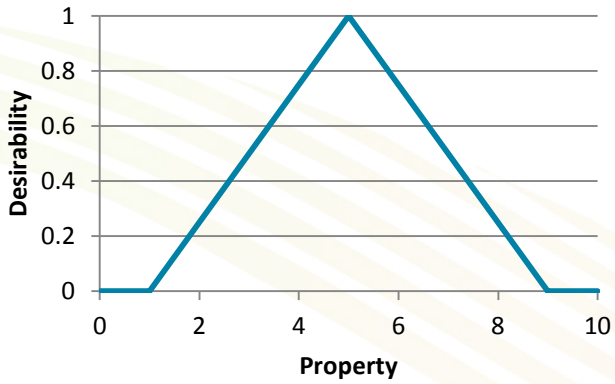


Trend: >8

* Harrington EC. (1965) Ind. Qual. Control. **21** p. 494

Approaches for MPO
Desirability Functions*

- Relate property values to how ‘desirable’ the outcome

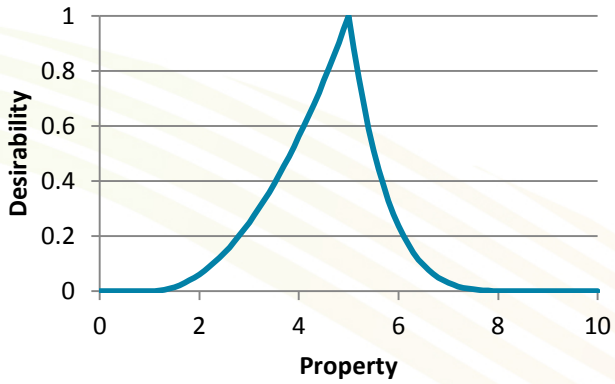


Ideal value: 5

* Harrington EC. (1965) Ind. Qual. Control. **21** p. 494

Approaches for MPO
Desirability Functions*

- Relate property values to how ‘desirable’ the outcome



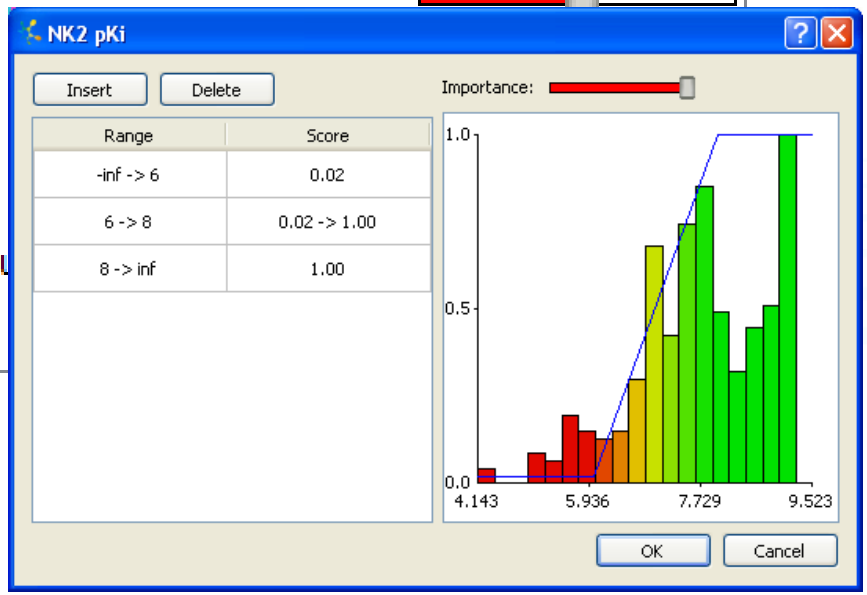
Non-linear, ideal value: 5
(Derringer Function)

- Combine multiple properties into ‘desirability index’
  - Additive:
  - Multiplicative:
- Very flexible approach allowing parameters to be weighted
- But, does not explicitly consider uncertainty

* Harrington EC. (1965) Ind. Qual. Control. **21** p. 494

Approaches for MPO
Probabilistic Scoring*

Profile	Desired Value	Importance
logS	≥ 1	
HIA category	+	
logP	0 -> 3.5	
BBB log([brain]:[blood])	-0.2 -> 1	
BBB category	+	
P-gp category	no	
hERG pIC50	≤ 5	
2C9 pKi	≤ 6	
2D6 affinity category	low mediu	
PPB90 category	low	



*M.D. Segall (2012) Curr. Pharm. Des. **18**(9) pp. 1292-1310

Approaches for MPO
Probabilistic Scoring*

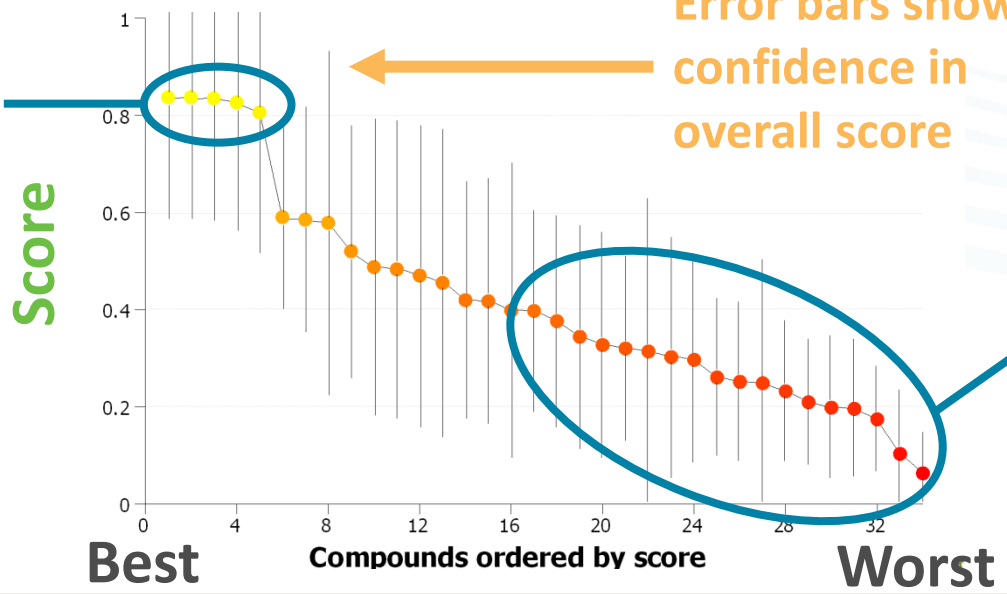
- **Property data**
  - Experimental or predicted
- **Criteria for success**
  - Relative importance
- **Uncertainties in data**
  - Experimental or statistical

- **Score (Likelihood of Success)**
- **Confidence in score**

Data do not separate these as error bars overlap

Error bars show confidence in overall score

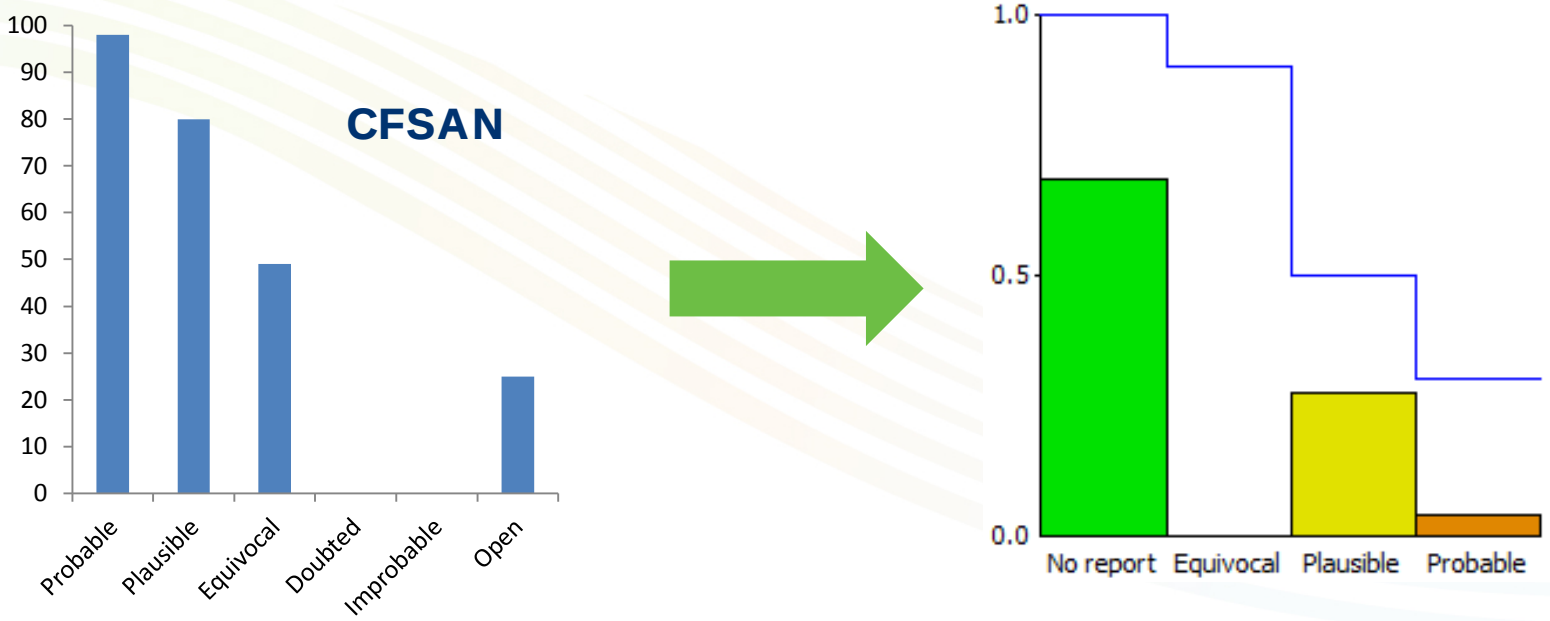
Bottom 50% may be rejected with confidence



*M.D. Segall (2012) Curr. Pharm. Des. **18**(9) pp. 1292-1310

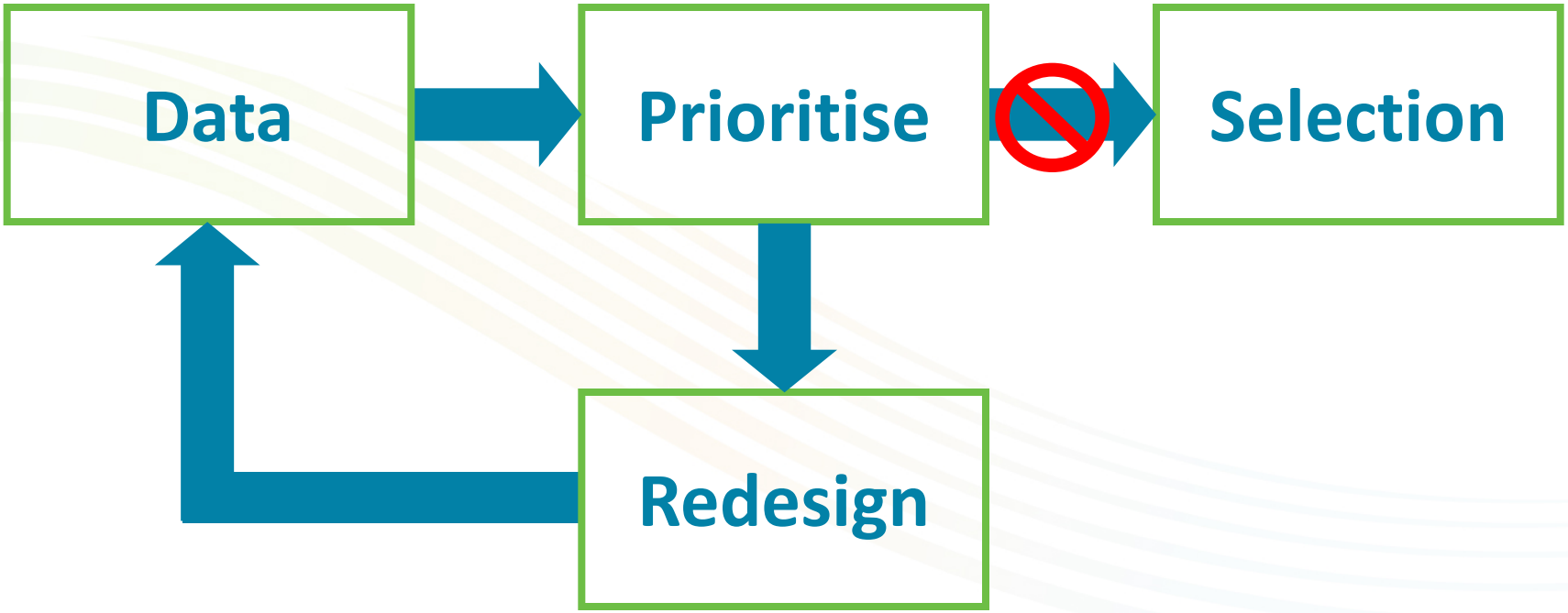
Application to Toxicity Alerts
E.g. Mutagenicity

- Determine desirability function by reference to validation results:



- Also need to take into account:
  - Impact of toxicity on objective of project
  - Stage of the project, e.g. opportunity to redesign to reduce risk

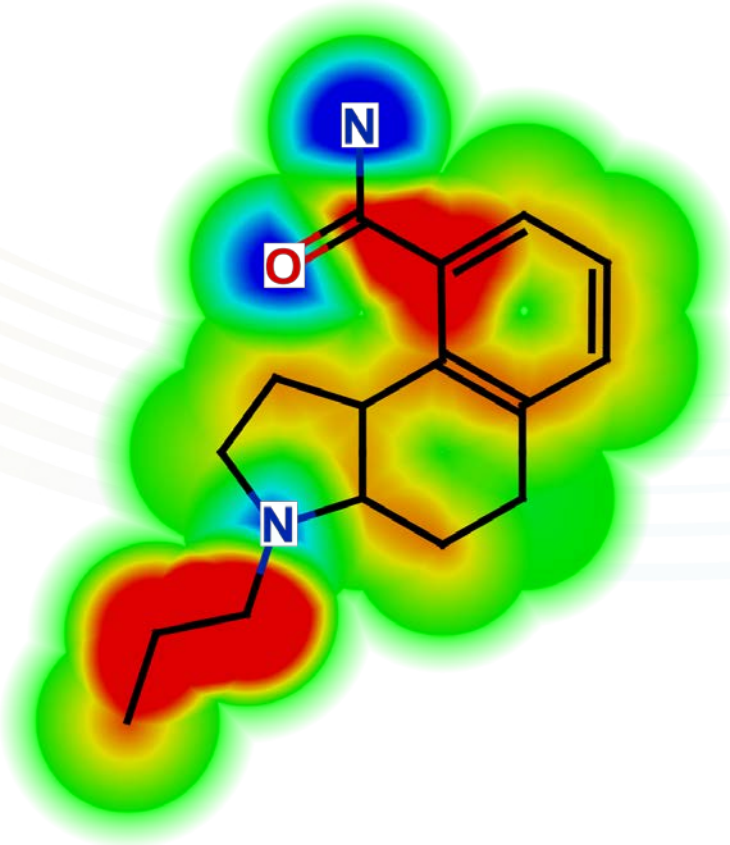
Guiding Interactive Redesign



Interpretation of a Model
The 'Glowing Molecule'

- Provides visual interpretation of structural influences on predicted properties
  - "Why is a property value predicted?"
  - "Where can I change this property?"
  - Interpret SAR
  - Guide efficient redesign of molecules

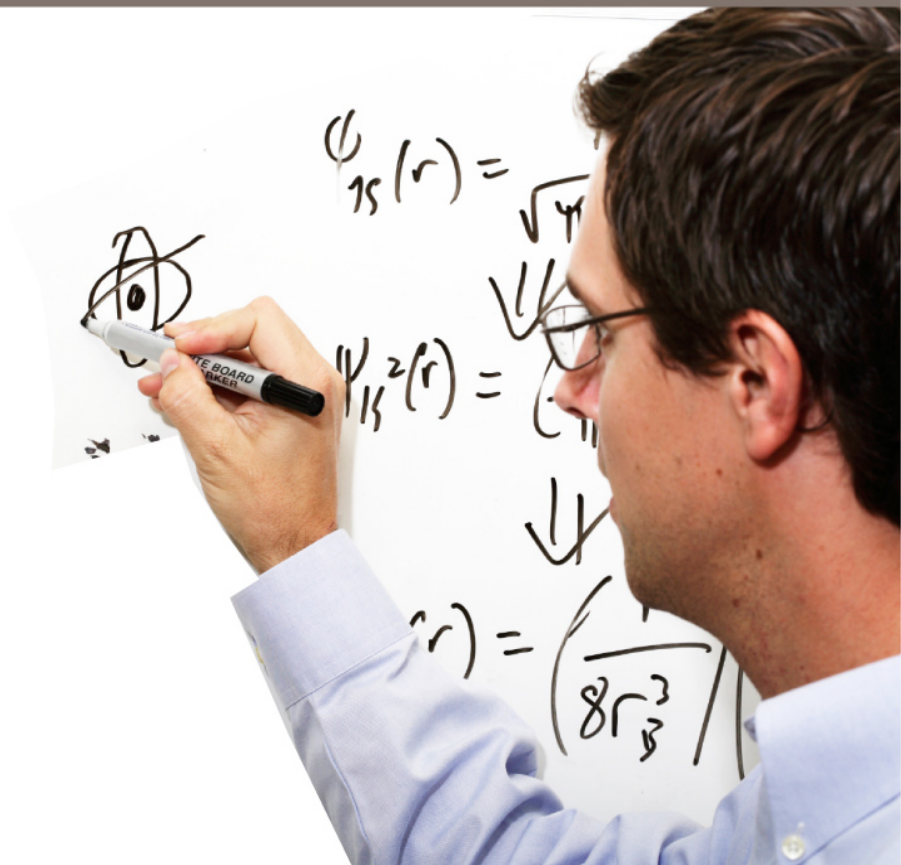
- Avoid Black Boxes



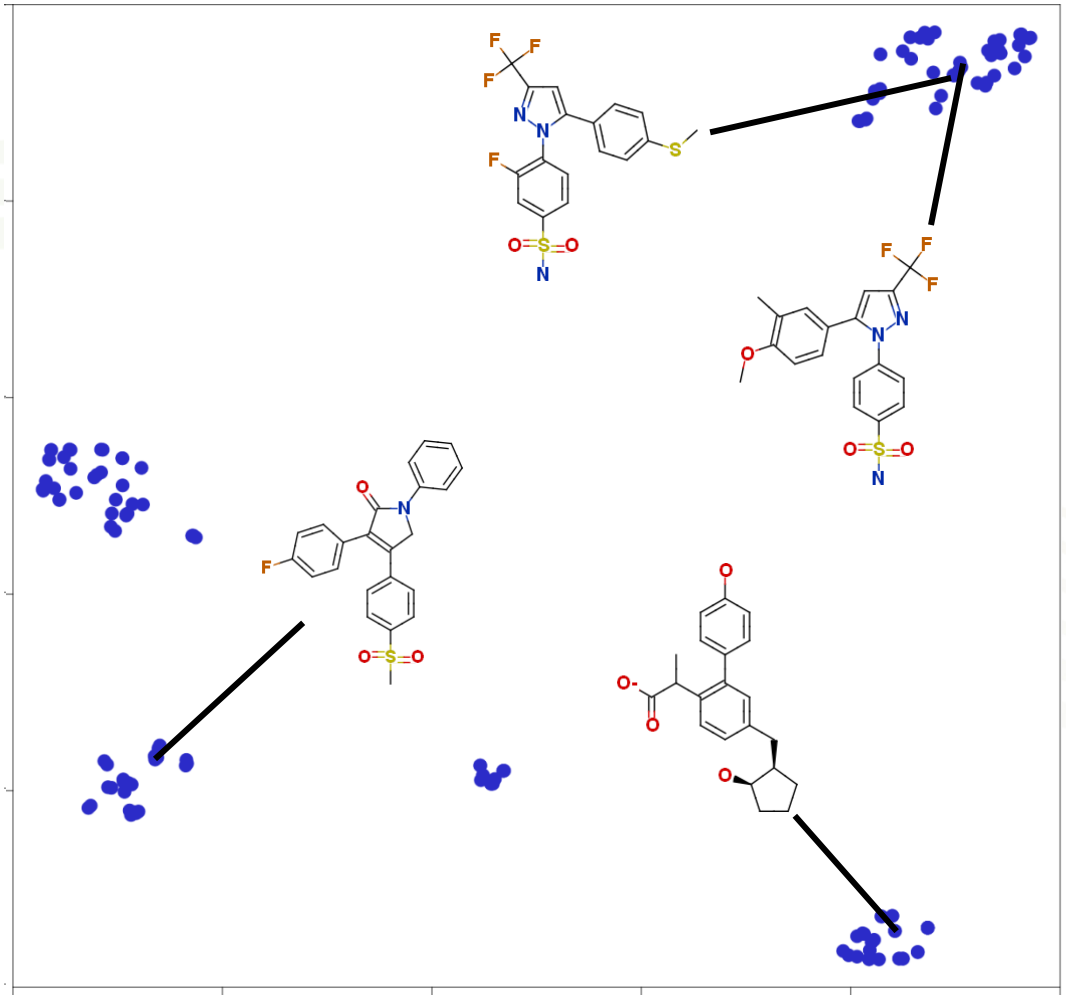
* Segall *et al.* (2009) Chem. & Biodiv. **6** p. 2144

Example Application
Exploring a COX2 screening library

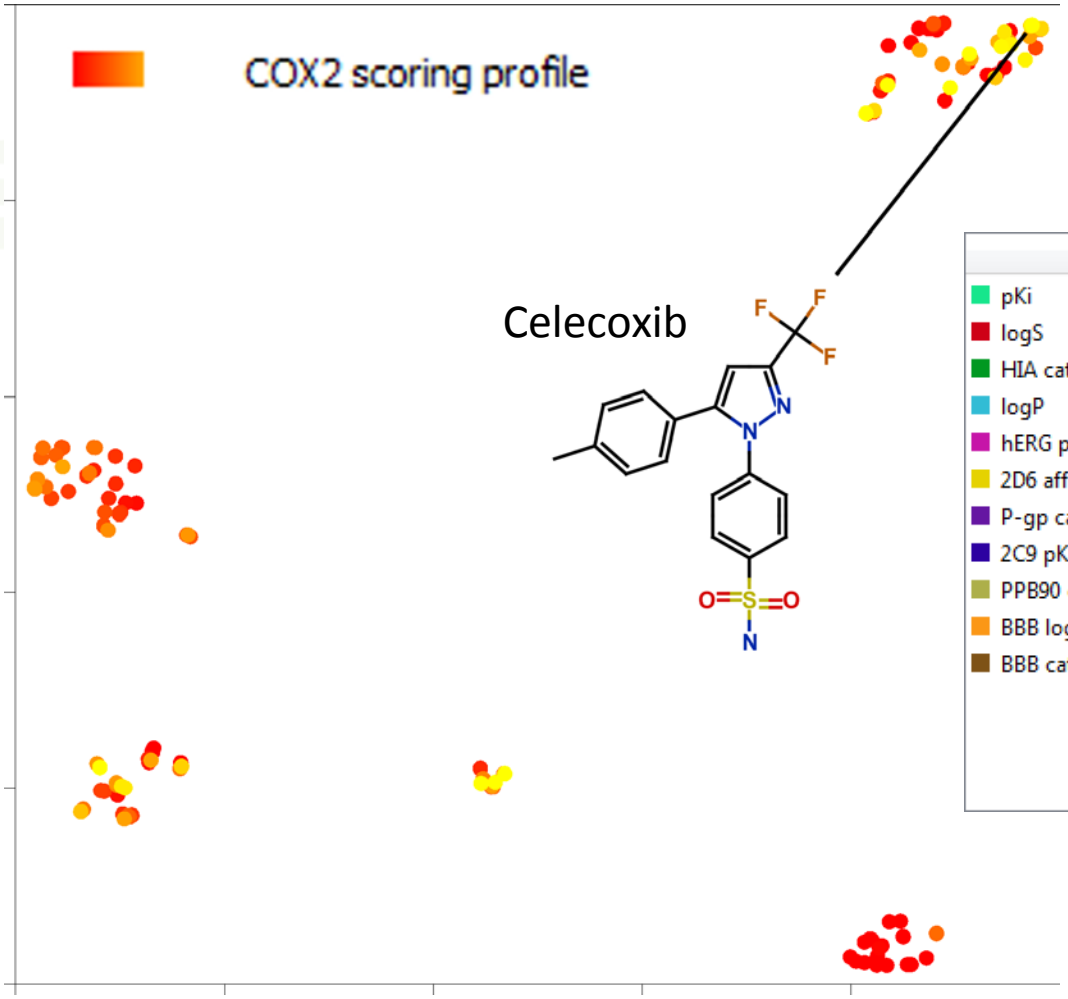
optibrium



COX2 library
Chemical space

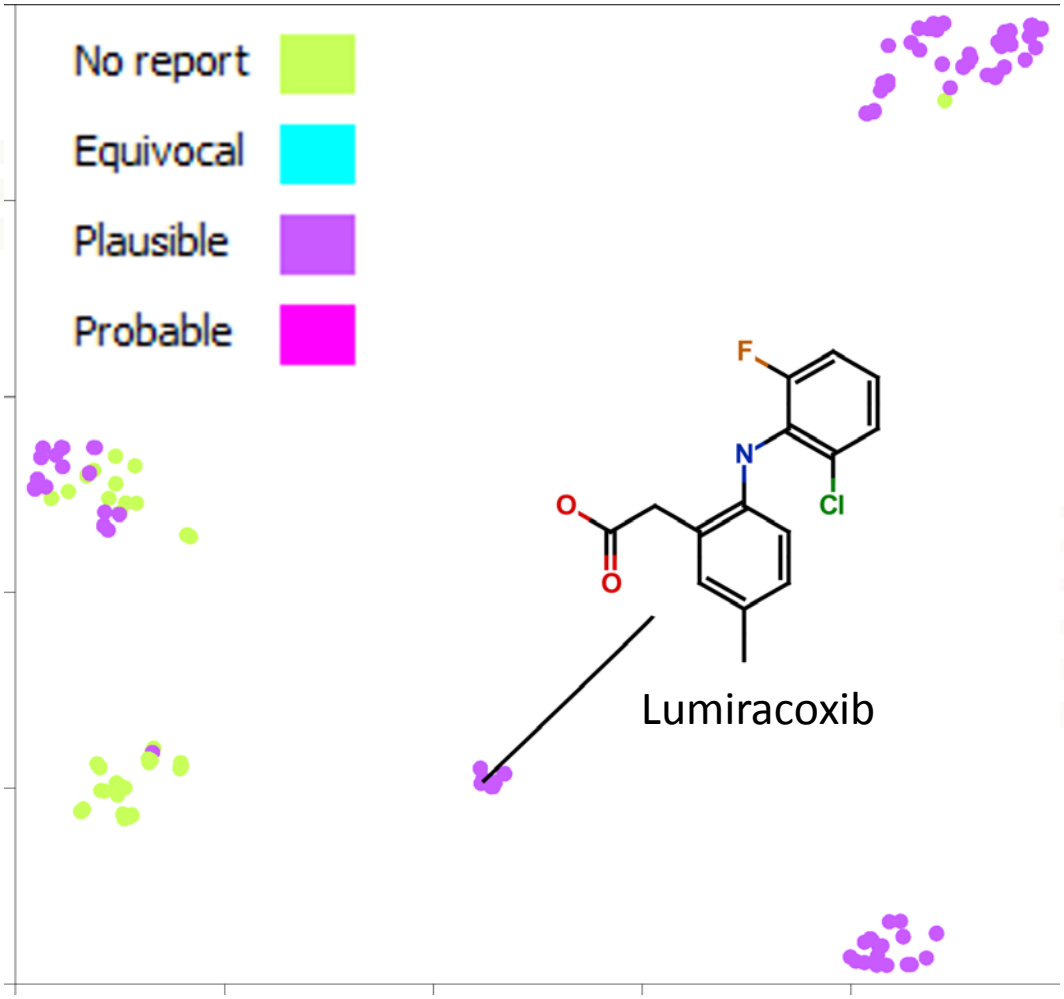


COX2 library
Scored excluding toxicity endpoints

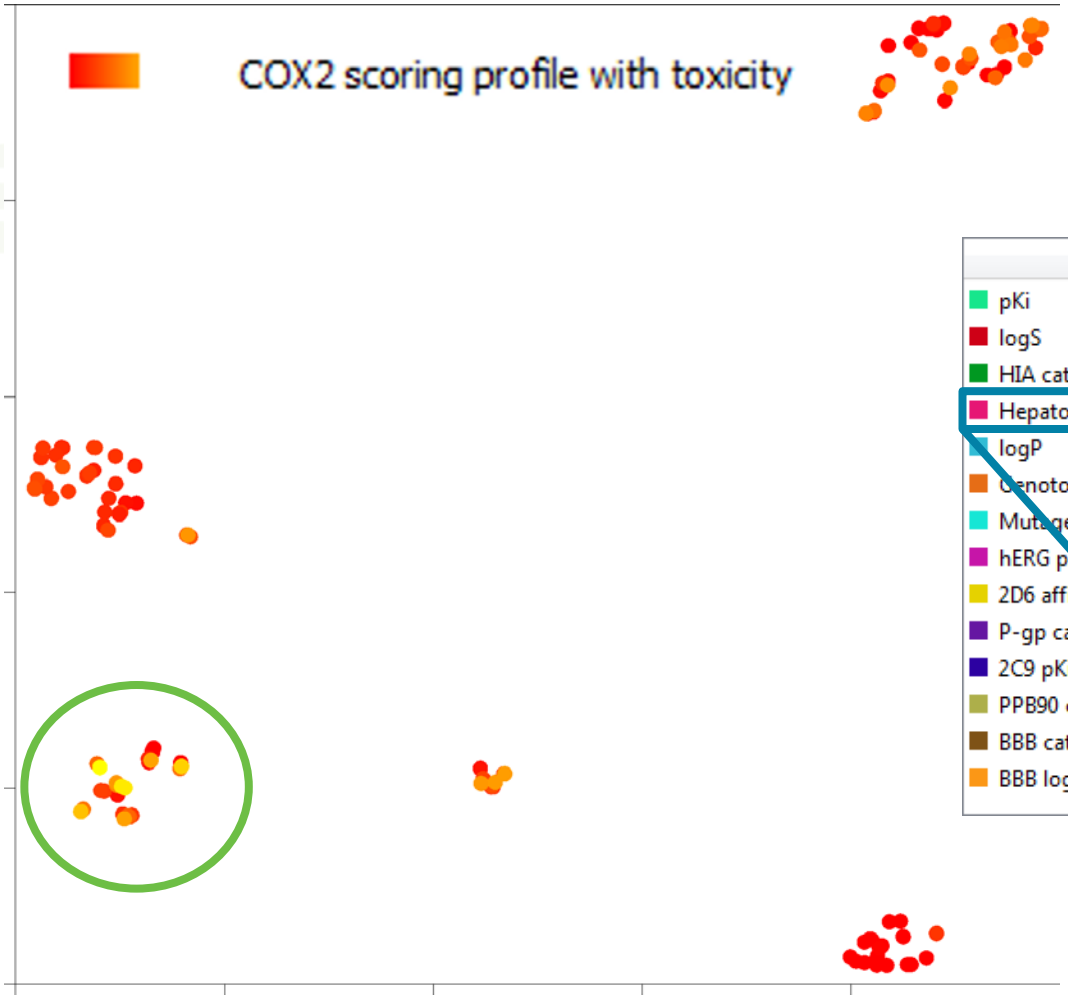


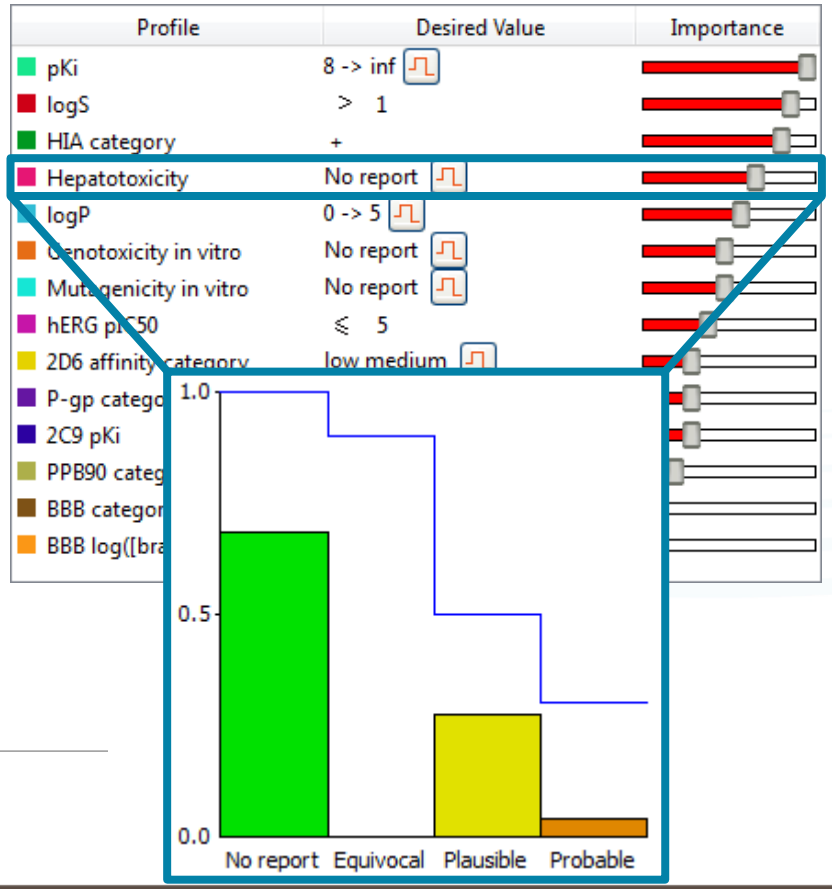
Profile	Desired Value	Importance
pKi	8 -> inf	
logS	> 1	
HIA category	+	
logP	0 -> 5	
hERG pIC50	⩽ 5	
2D6 affinity category	low medium	
P-gp category	no	
2C9 pKi	⩽ 6	
PPB90 category	low	
BBB log([brain]:[blood])	⩽ -0.5	
BBB category	-	

COX2 library
Predicted hepatotoxicity

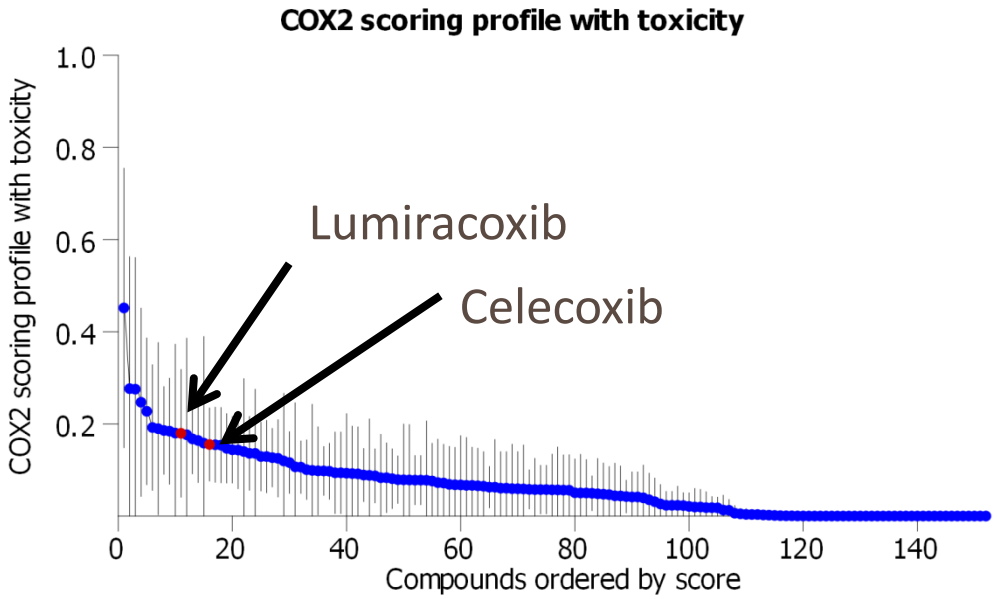


COX2 library
Scored including toxicity endpoints





But wait…
Wouldn't we miss Celecoxib?!

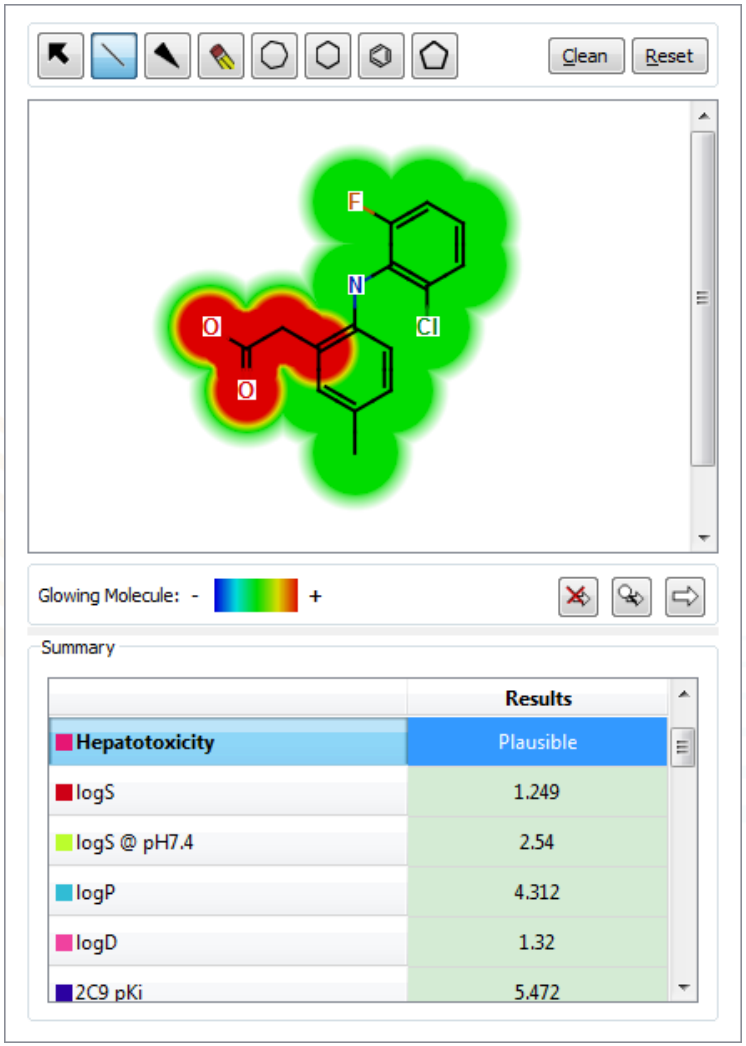


- Celecoxib and Lumiracoxib would not be rejected outright
  - Highlighted hazard, confirm experimentally and consider context
- Celecoxib does exhibit signs of hepatotoxicity, but is 'saved' by its low dose and high therapeutic index*

*Moore *et al.* (2005) *Arthritis Res. Ther.* 7, R644-R665

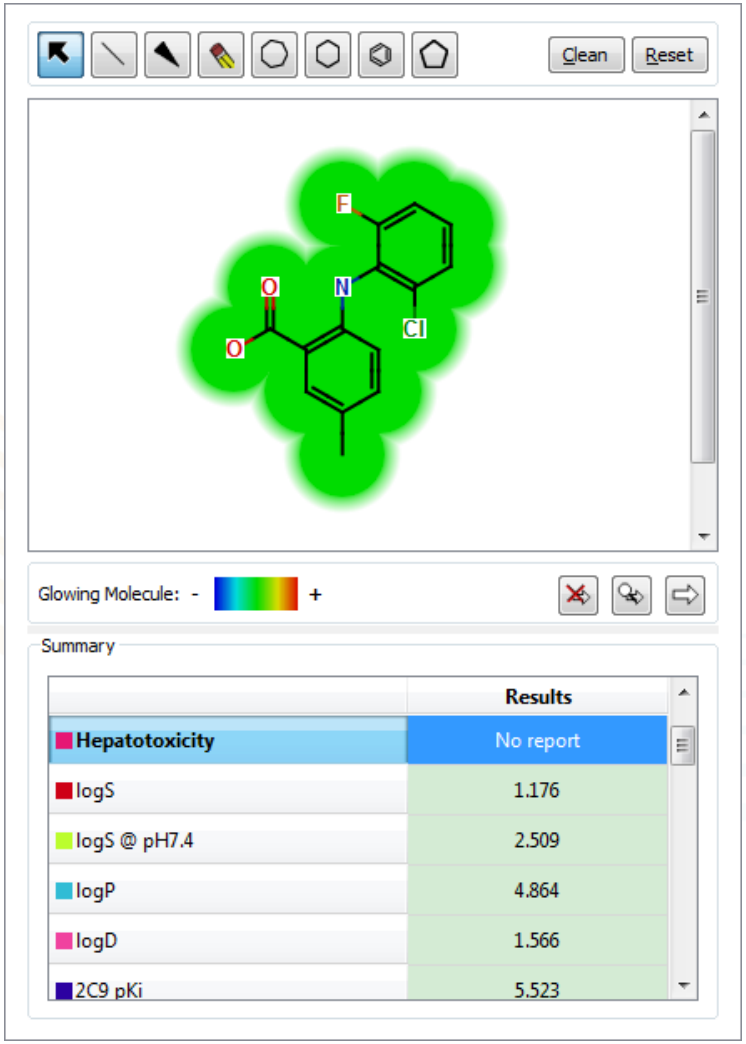
Consider Redesign Strategies
Lumiracoxib

- Glowing molecule highlights 2-Arylacetic acid alert
- Interactively explore strategies for reducing risk
  - Monitor changes in multiple properties simultaneously



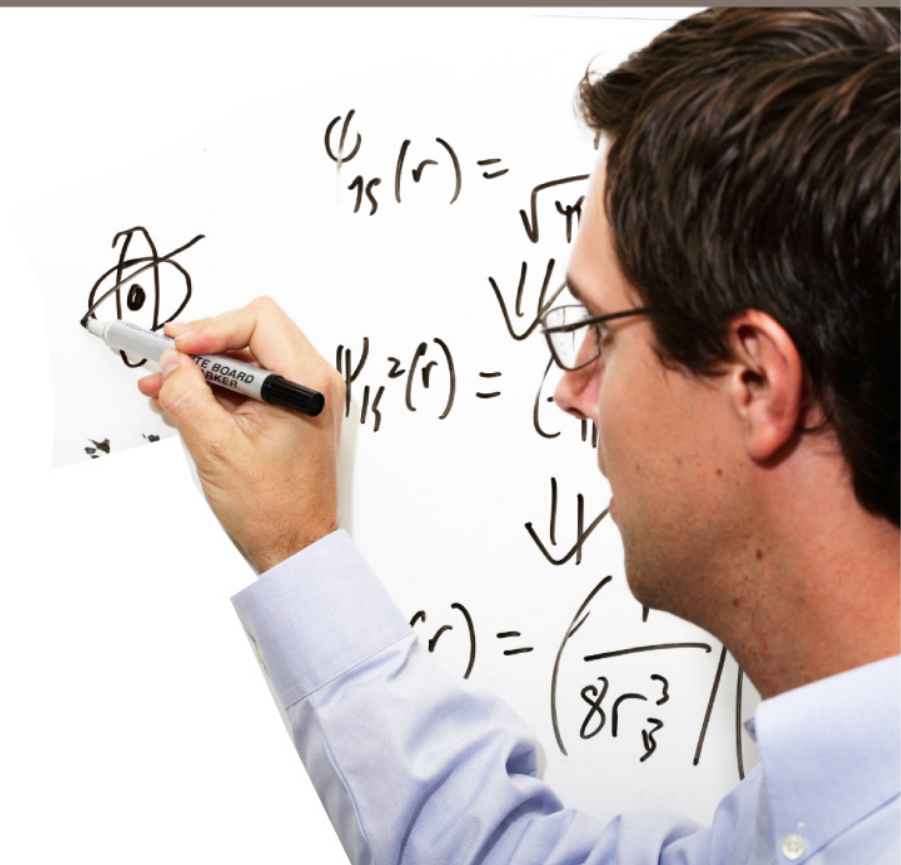
Consider Redesign Strategies
Lumiracoxib

- Glowing molecule highlights 2-Arylacetic acid alert
- Interactively explore strategies for reducing risk
  - Monitor changes in multiple properties simultaneously



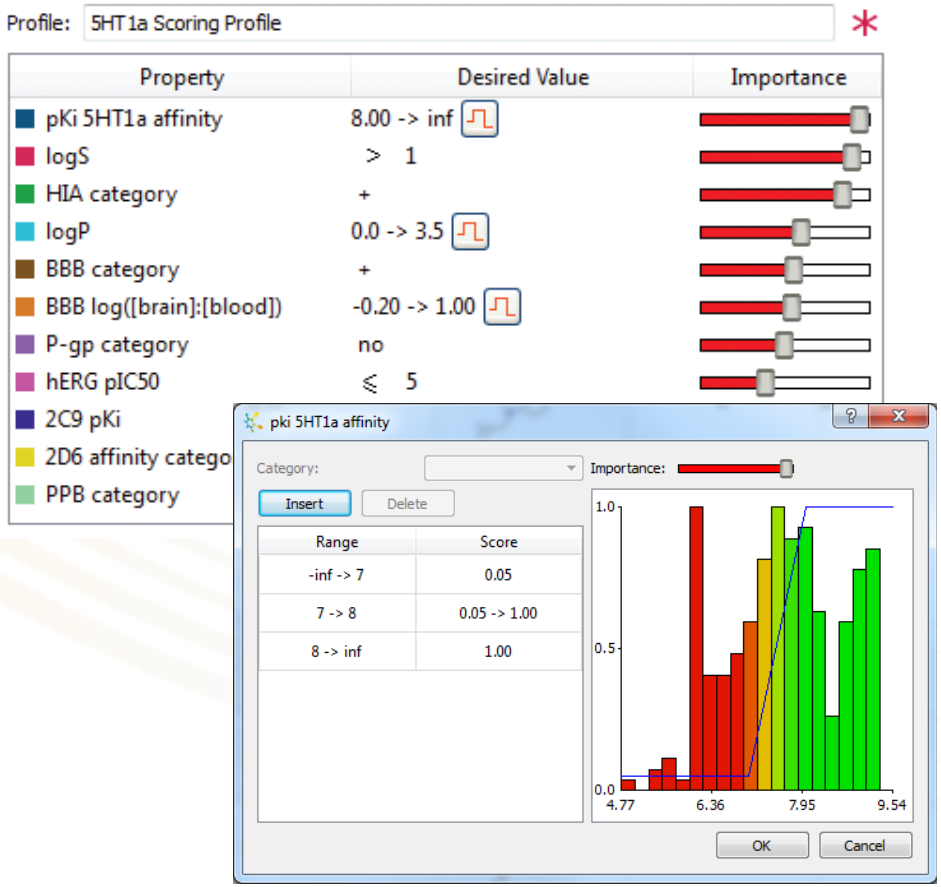
Introduction to StarDrop and the Derek Nexus module

optibrium



StarDrop Helps to Guide Decisions
From selection… to design

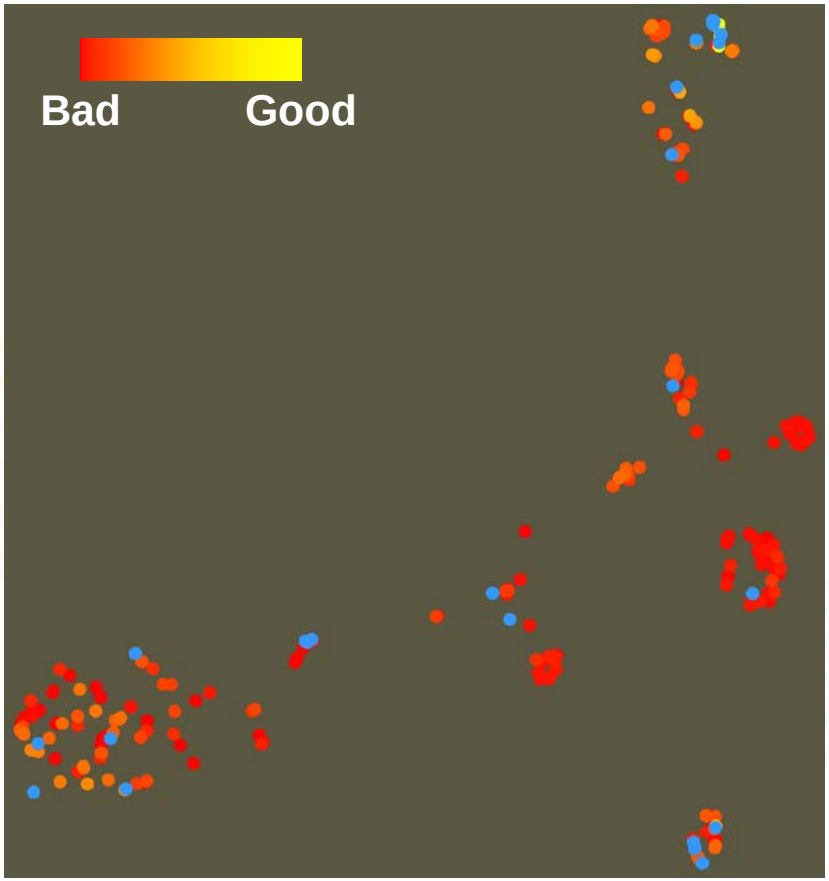
- Probabilistic Scoring*
  - User-defined profile and weights
  - Use data from any source
  - Allow for uncertainty
  - Score for likelihood of success
- Chemical Space and Selection
  - View property distributions across chemical diversity
  - Balance quality and diversity
- Glowing Molecule
  - Interactively explore new ideas
  - Link compounds structure with properties
- Interactive Visualisation
  - R-group analysis
  - Matched Molecular Pair analysis



*M.D. Segall (2012) Curr. Pharm. Des. **18**(9) pp. 1292-1310

StarDrop Helps to Guide Decisions
From selection… to design

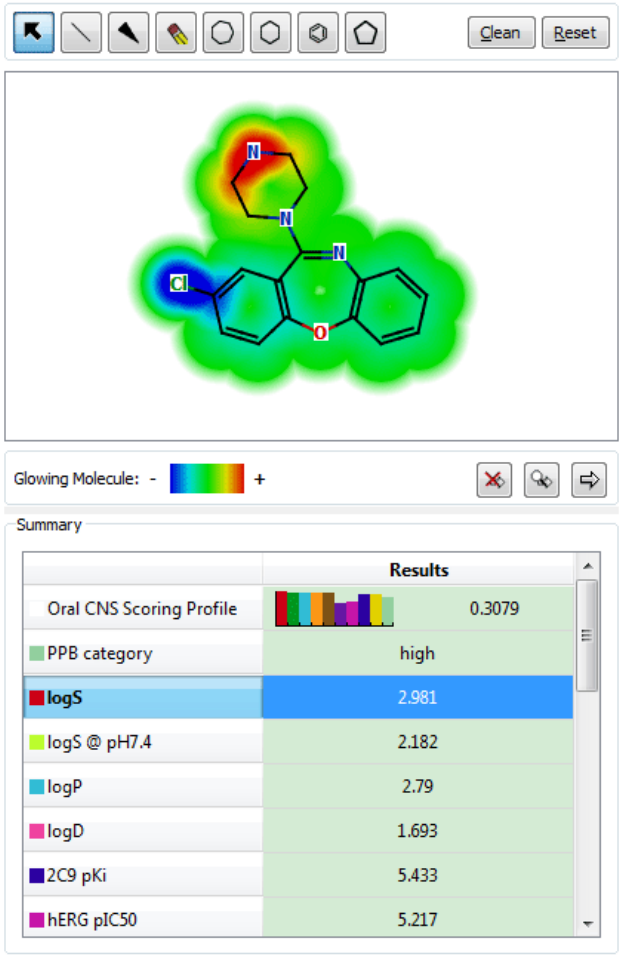
- Probabilistic Scoring
  - User-defined profile and weights
  - Use data from any source
  - Allow for uncertainty
  - Score for likelihood of success
- Chemical Space and Selection*
  - View property distributions across chemical diversity
  - Balance quality and diversity
- Glowing Molecule
  - Interactively explore new ideas
  - Link compounds structure with properties
- Interactive Visualisation
  - R-group analysis
  - Matched Molecular Pair analysis



 *M.D. Segall *et al.* (2006) Expert Opin. Drug. Metab. Tox. **2**(2) pp. 325-337

StarDrop Helps to Guide Decisions
From selection… to design

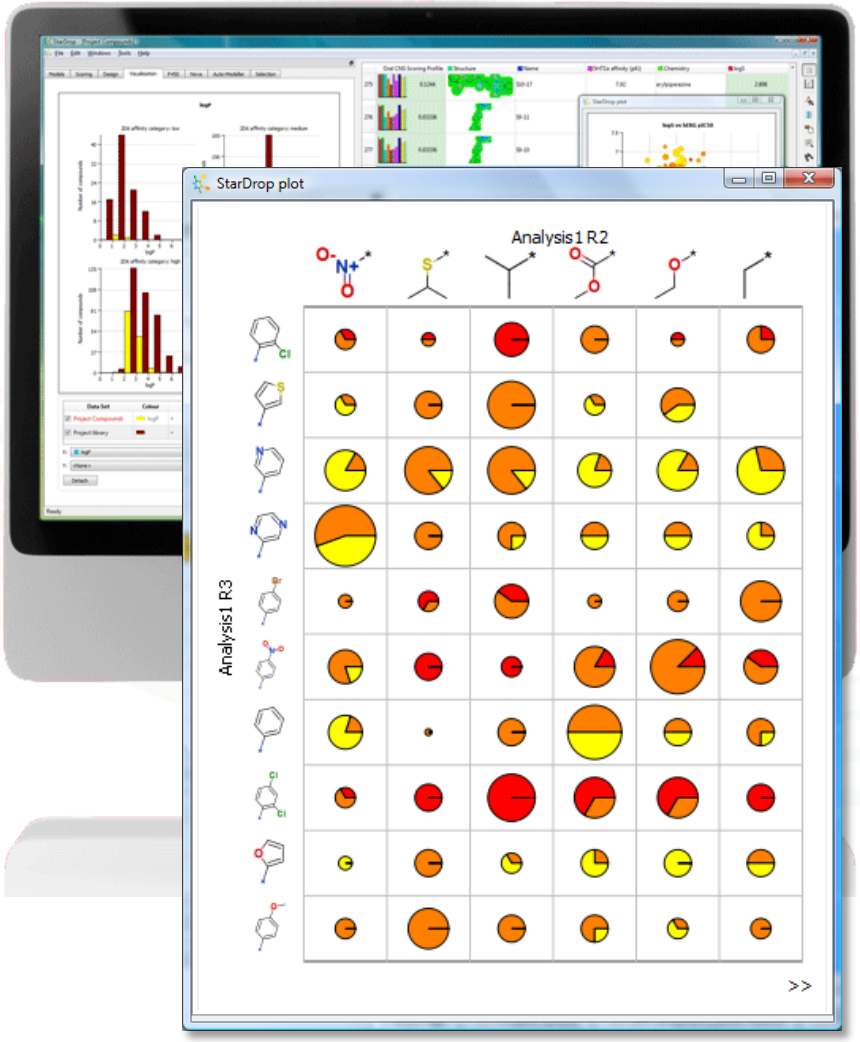
- Probabilistic Scoring
  - User-defined profile and weights
  - Use data from any source
  - Allow for uncertainty
  - Score for likelihood of success
- Chemical Space and Selection
  - View property distributions across chemical diversity
  - Balance quality and diversity
- Glowing Molecule*
  - Interactively explore new ideas
  - Link compounds structure with properties
- Interactive Visualisation
  - R-group analysis
  - Matched Molecular Pair analysis



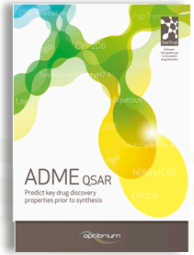
*M.D. Segall *et al.* (2009) Chem. & Biodiv. **6**(11) p. 2144-2151

StarDrop Helps to Guide Decisions
From selection… to design

- Probabilistic Scoring
  - User-defined profile and weights
  - Use data from any source
  - Allow for uncertainty
  - Score for likelihood of success
- Chemical Space and Selection
  - View property distributions across chemical diversity
  - Balance quality and diversity
- Glowing Molecule
  - Interactively explore new ideas
  - Link compounds structure with properties
- Interactive Visualisation
  - R-group analysis
  - Matched Molecular Pair analysis

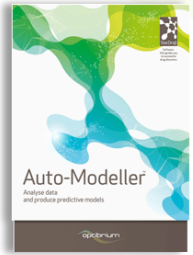


StarDrop Plug-in Modules and Integration
Extend Core Capabilities



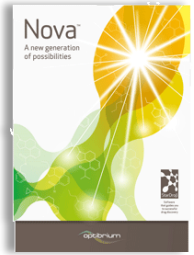
ADME QSAR

High quality predictive models of key ADME properties



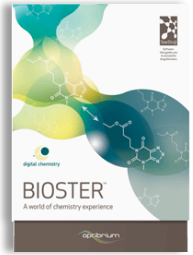
Auto-Modeller

Build and validate robust models tailored to your chemistry



Nova

Generate and prioritise new, relevant compound ideas



BIOSTER™

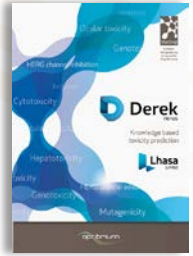
Explore >20k precedented transformations with the Nova module

P450

QM simulations identify sites of metabolism and lability for major P450s

torch3D™

Understand and apply 3D SAR to identify and optimise novel actives



Derek Nexus™

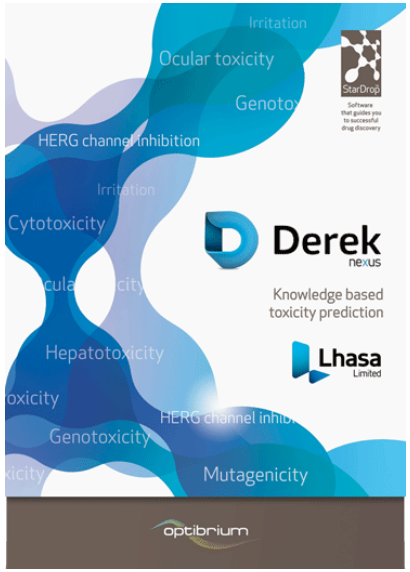
Knowledge-based prediction of >40 toxicity endpoints

MPO Explorer™

Develop multi-parameter optimisation strategies

Derek Nexus™ Module for StarDrop
Differences with full Derek Nexus

- Derek Nexus for StarDrop provides unique features for medicinal chemists and drug discovery projects, e.g.
  - Visualisation to explore toxicity risk of different chemistries
  - Probabilistic scoring to balance toxicity risk against other factors
  - Interactive design with Glowing Molecule to guide redesign and reduce risk of toxicity



- The full Derek Nexus platform from Lhasa Limited provides access to full Derek knowledge base for expert toxicologists
  - Information on mechanism of action, biological data and references
  - Detailed annotation of structural alerts
  - Helps to design toxicology experiments

- Reporting feature in StarDrop helps collaboration between drug discovery projects and preclinical toxicology

Conclusion

- Addressing toxicity early in the drug discovery process is key to improving success rate and productivity
- Knowledge based predictions provide a reliable way to identify toxicity hazards (potential risk)
- Results need to be used in context of other requirements of a successful drug
- Need to take confidence into account
  - Avoid rejecting good compounds due to uncertain data
- Reference:
  - Segall and Barber, Drug Discov. Today **19** (2014), pp. 688-693
  - Download (p)reprint from www.optibrium.com/community/publications