



Derek
nexus

The Expert System
for ICH M7



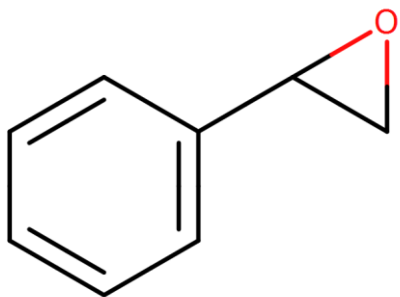
Agenda

- This session covers:
 - Structural alerts for *in vitro* mutagenicity
 - How Lhasa generates structural alerts
 - Reasoning between evidence
 - Improved predictions through data sharing
 - Negative predictions
 - Supporting expert review
 - Conclusions



Structural alerts for *in vitro* mutagenicity

Structural alerts within Derek Nexus

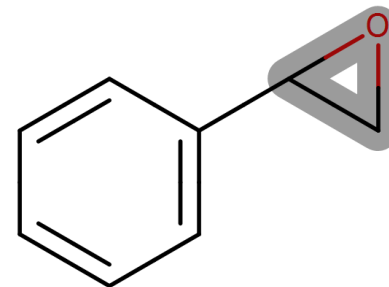


Query

Derek Nexus



in vitro
mutagenicity



Structural alert
identified

▲ **Derek KB 2018 1.1 [Certified by: Lhasa Limited, Leeds, Yorkshire, UK]**

▲ **Mutagenicity in vitro**

▲ **bacterium - PROBABLE**

Alert - 019: Epoxide

Example - styrene oxide

▼ Comments

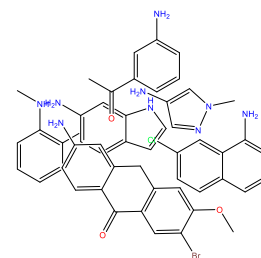
Chromosome damage (clastogenicity): *in vitro* chromosome aberration test, *in vivo* micronucleus test
Mutagenicity: Ames test, *in vivo* transgenic rodent mutation assay

Epoxides are electrophilic compounds that readily bind to DNA [Citti et al, Sugiura and Goto]. As a consequence, they may exhibit mutagenicity in the Ames test, generally in strains TA100 and TA1535 without S9 mix [Canter et al, von der Hude et al, Sugiura and Goto, Tamura et al, Wade et al]. The effect of S9 mix on the mutagenic response varies depending, for example, on the susceptibility of the test chemical to detoxification by epoxide hydrolases and glutathione S-transferase present in the S9 mix [Castelain et al].

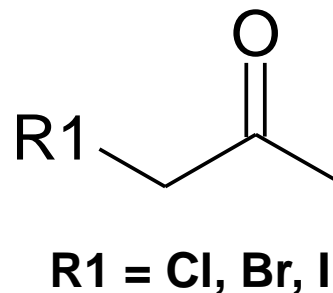
How do we generate alerts



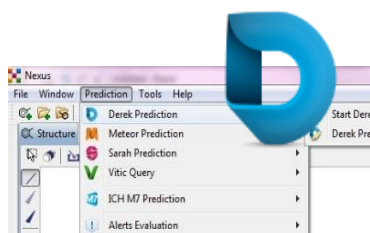
Aggregate data
from multiple sources



Experts examine
trends in data



Identify
SARs



**Robust and
transparent predictions**

Bacterial Mutagenicity

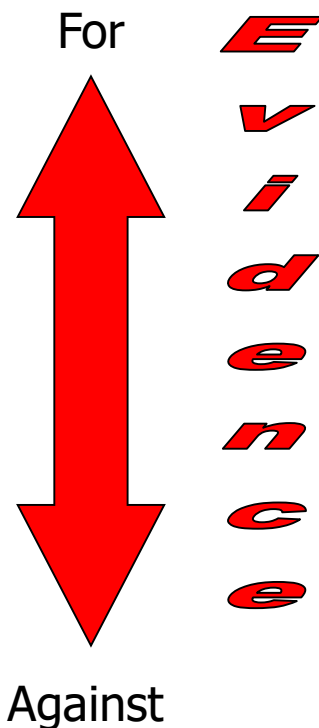
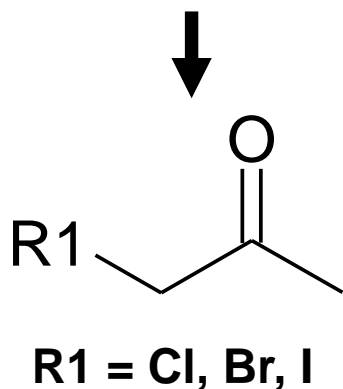
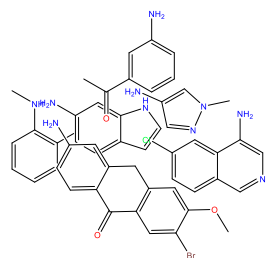
- Primary data used for alert development include:
 - Ames test data in both *Salmonella typhimurium* and *Escherichia coli*.
 - Supporting data can include data from other *in vivo* and *in vitro* assays
- Transparent predictions supports expert review
 - Expert comments with references
- Derek Nexus' Knowledge base 2018.1:
 - Over 130 alerts for *in vitro* bacterial mutagenicity
 - Developed over 30 years



Reasoning and Likelihood Levels



Likelihood Levels



- Certain
- Probable
- Plausible
- Equivocal
- Doubted
- Improbable
- Impossible

- Reasoning considers evidence outlined in a set of rules to provide a logical outcome.
- Reasoning rules are present because an alert might not be appropriate in every situation.

Reasoning Rules

Consider:

If [Rain] is [Certain] then [Getting Wet] is [Plausible]

Condition:

What must happen
and how much

Action:

What will happen and how
likely it is to happen



Absolute Reasoning Rules

Consider:


What if you have an umbrella?




If [Rain] is [Certain] then [Getting Wet] is [X]

If [Umbrella] is [Certain] then [X] is [Improbable]


If [Umbrella] is [Impossible] then [X] is [Plausible]

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▲  Mutagenicity in vitro

▲  bacterium - PROBABLE

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 Example - styrene oxide

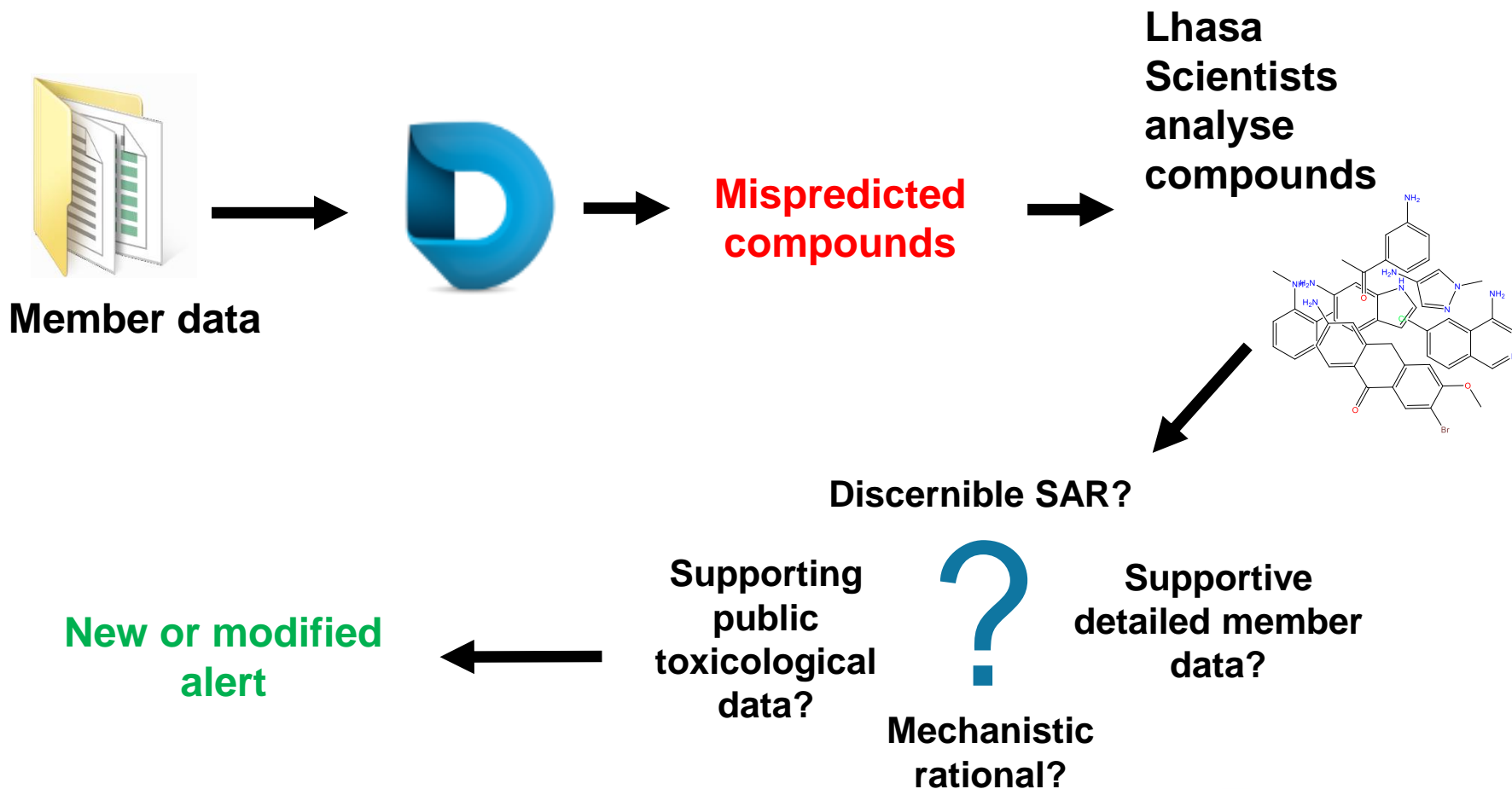


Improving predictions via data sharing

Why is data sharing important?

- Encourages **collaboration** which benefits the scientific community
- Gaps in the chemical space covered by *in silico* models can exist. By donating proprietary data, these gaps can be filled, and allows us to:
 - Model chemical space unique to each member
 - Improve predictivity in the chemical space most important to members
 - Generalise models for mutual benefit

How do we analyse member data?



Case study: Mutagenicity

- The performance of the mutagenicity endpoint was assessed using some proprietary data from members.
- The endpoint predicted well for public data, but sensitivity and positive predictivity were much lower for the members' data set:

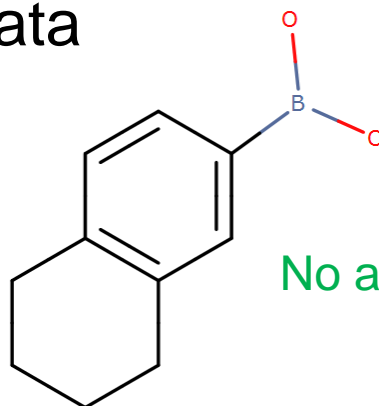
	Mutagenicity									
	Metrics (%)					Results				
Data set	Se	Sp	PP	NP	Acc	TP	FP	TN	FN	Total
Public	83	75	79	79	79	2908	762	2247	595	6512
Member	59	88	60	88	82	168	114	862	117	1261

- From the members' dataset **5 new alerts** were written and **4 existing alerts were modified**

Alert example

Alert 746: Arylboronic acid or derivative

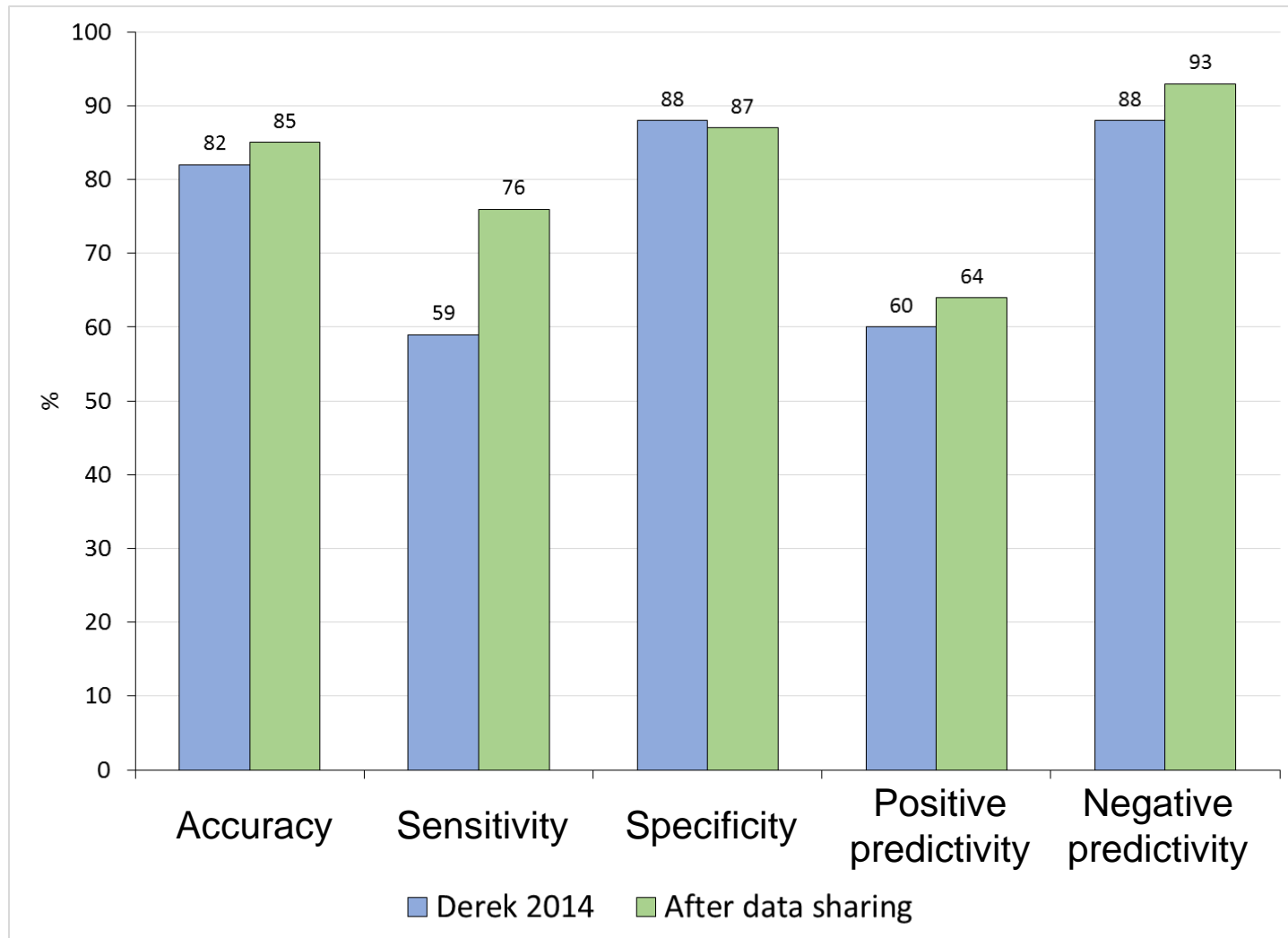
- Alert was made **more specific** by:
 - Narrowing the scope to exclude aryl boronic acids with bulky para substituents
 - Alert will also no longer fire if there is a fused non-aromatic ring at the para position
- This reduced the number of false positives by **27%** when tested against the members' data, and by **6%** when tested against public data



No alert fires

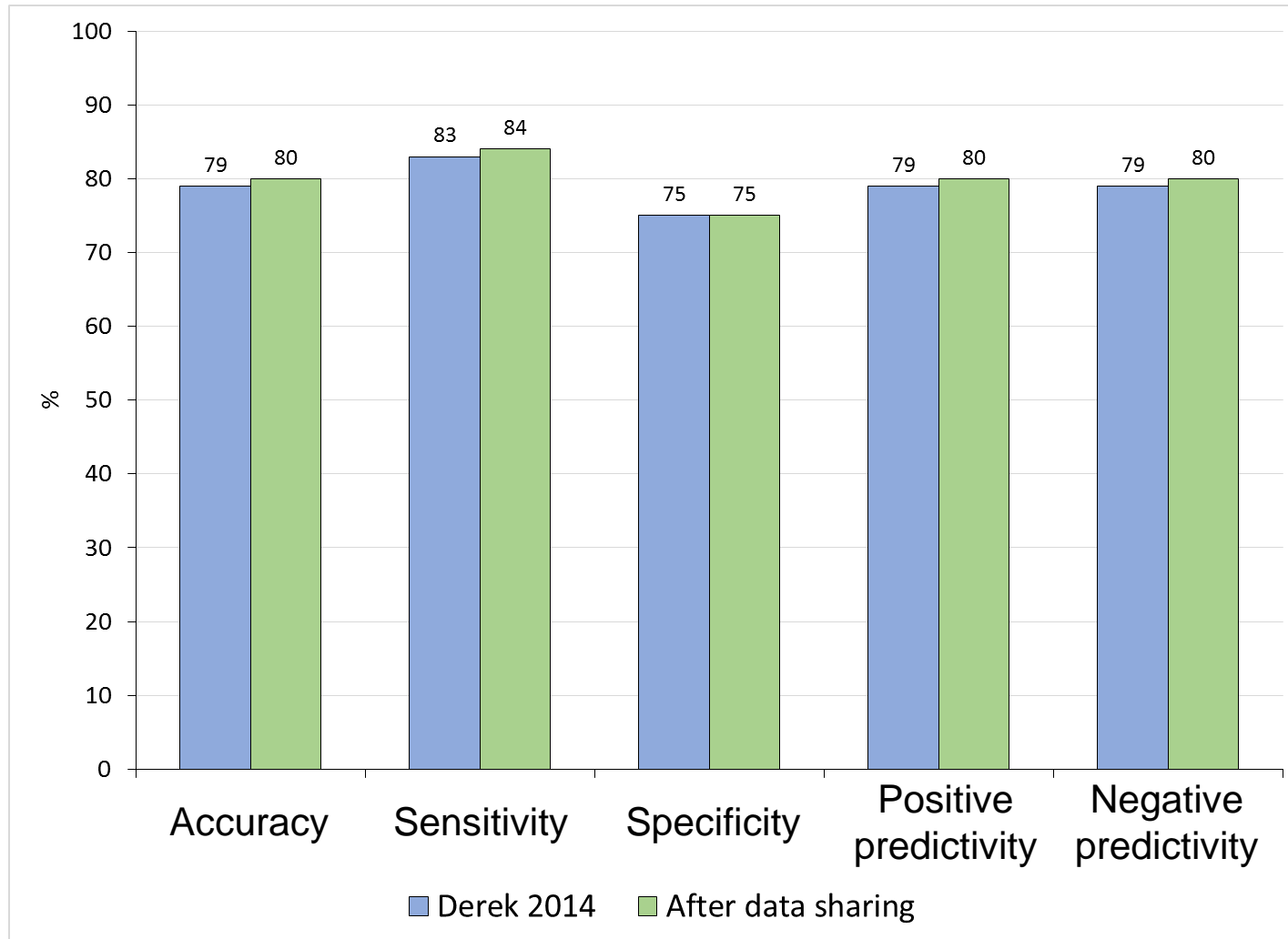
Case study: Mutagenicity results

Results – Member Data



Case study: Mutagenicity results

Results – Public data



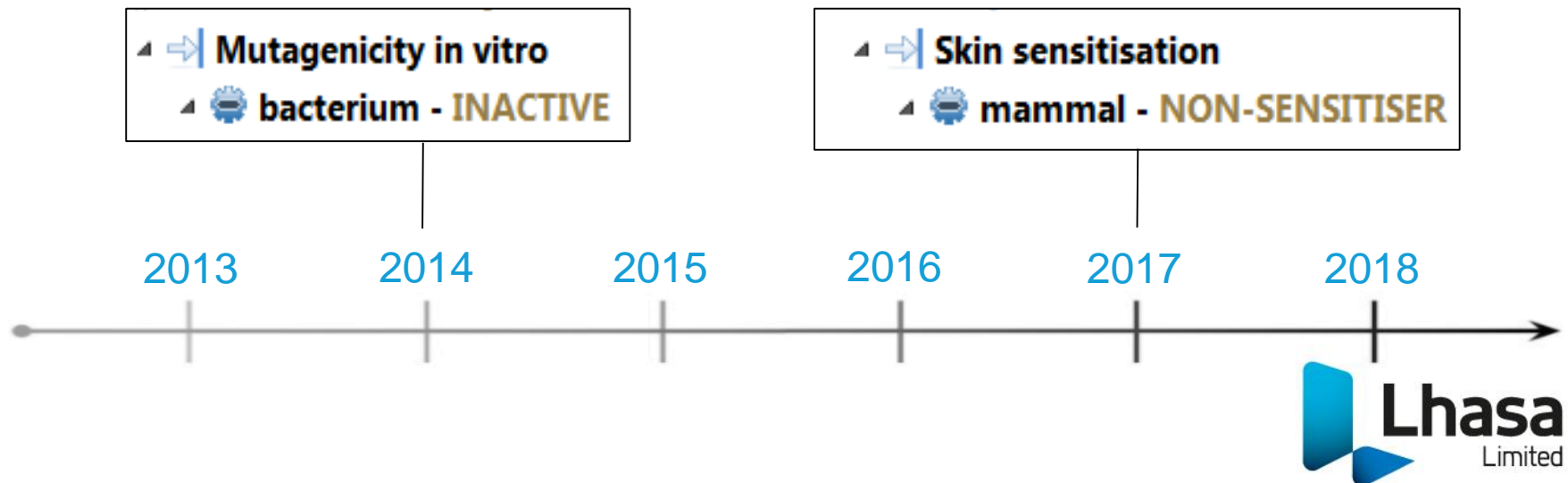


NEGATIVE PREDICTIONS

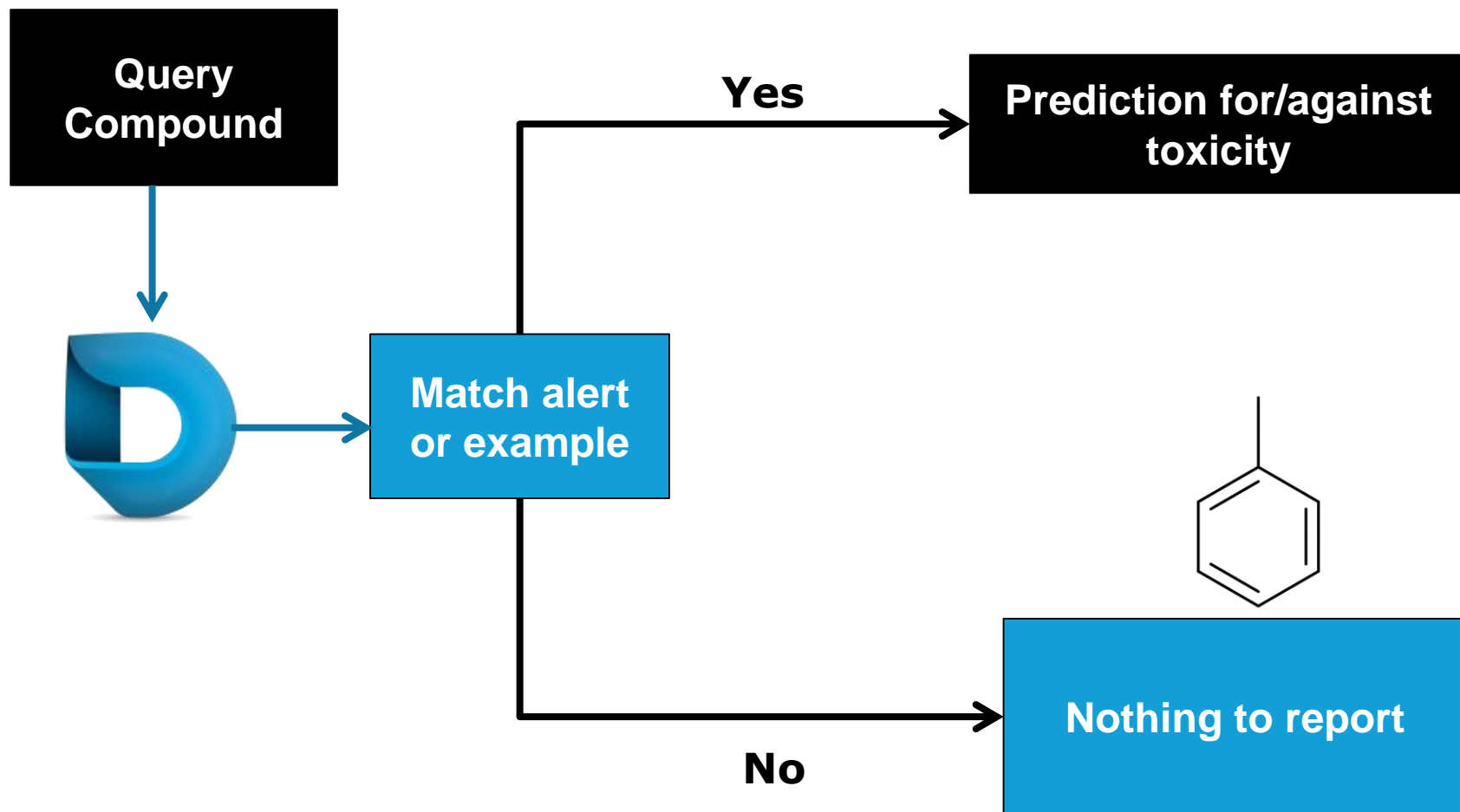


Why do we need negative predictions?

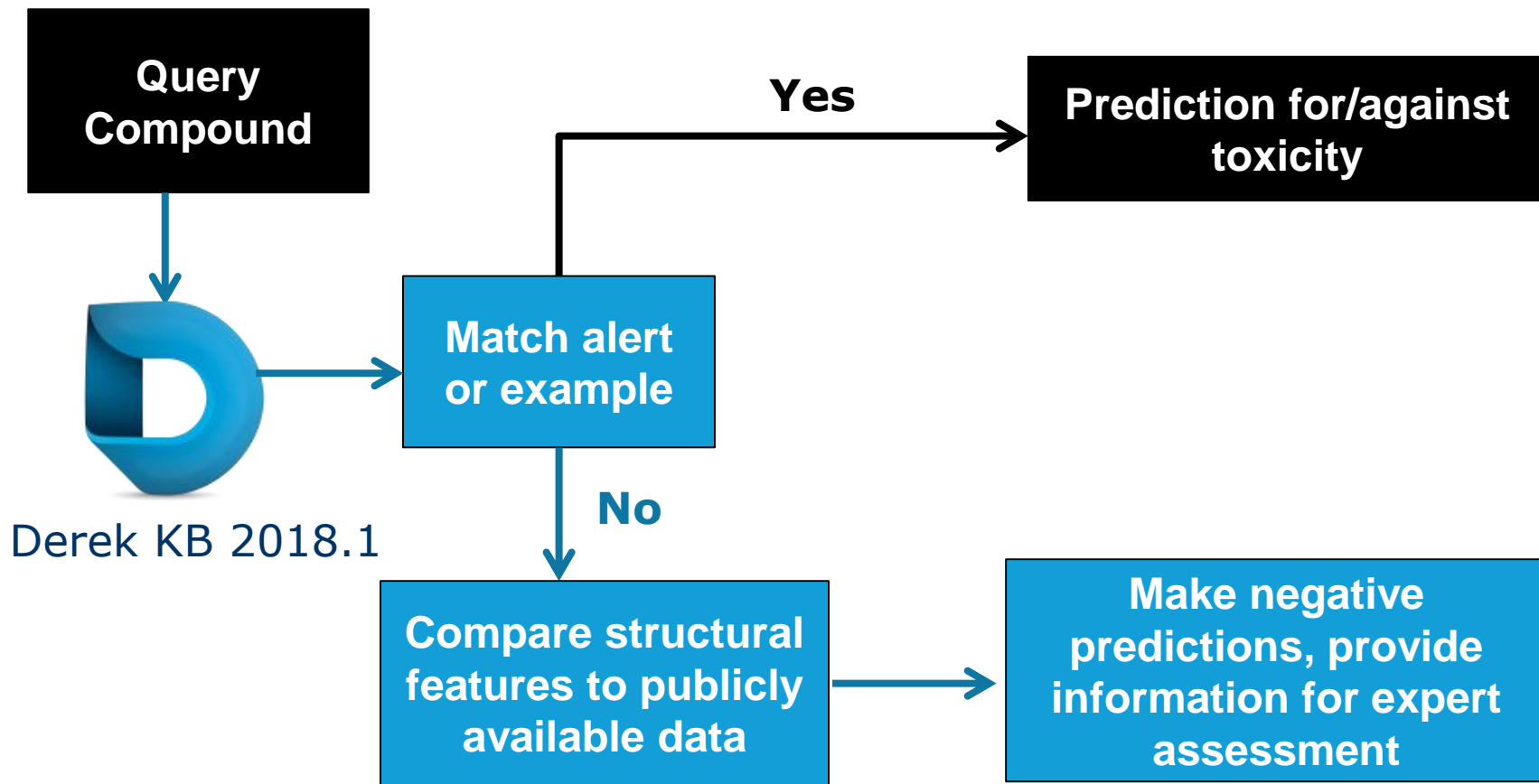
- Previously, a lack of alerts firing would always lead to this:
 - ✗ Nothing to report at this reasoning level
- For endpoints that are well developed, we wanted to provide a stronger prediction, and provide more information for expert review:



Workflow without negative predictions

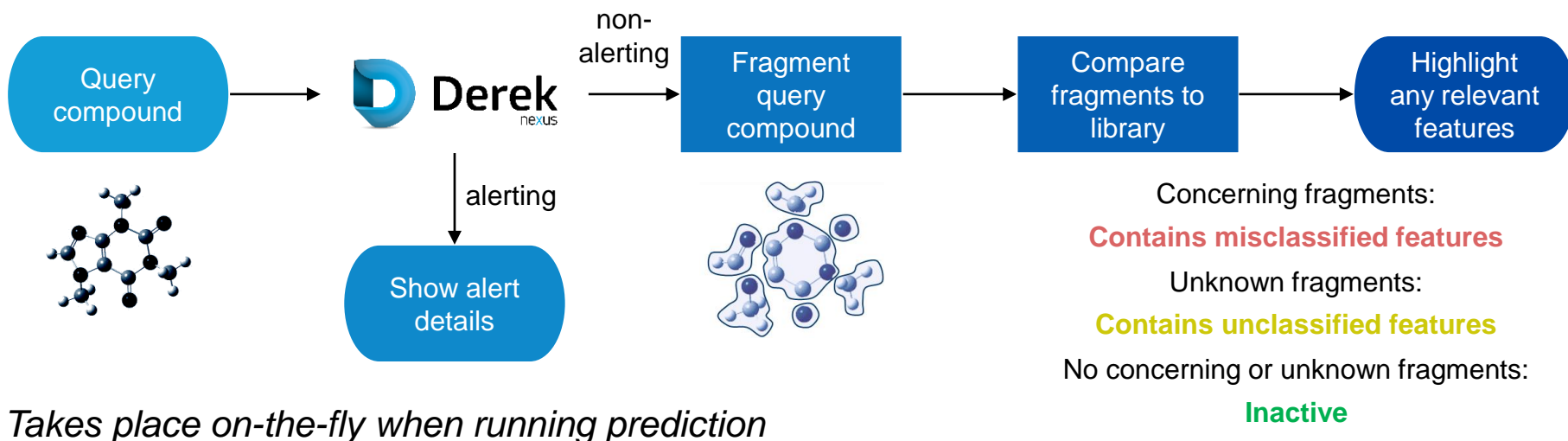
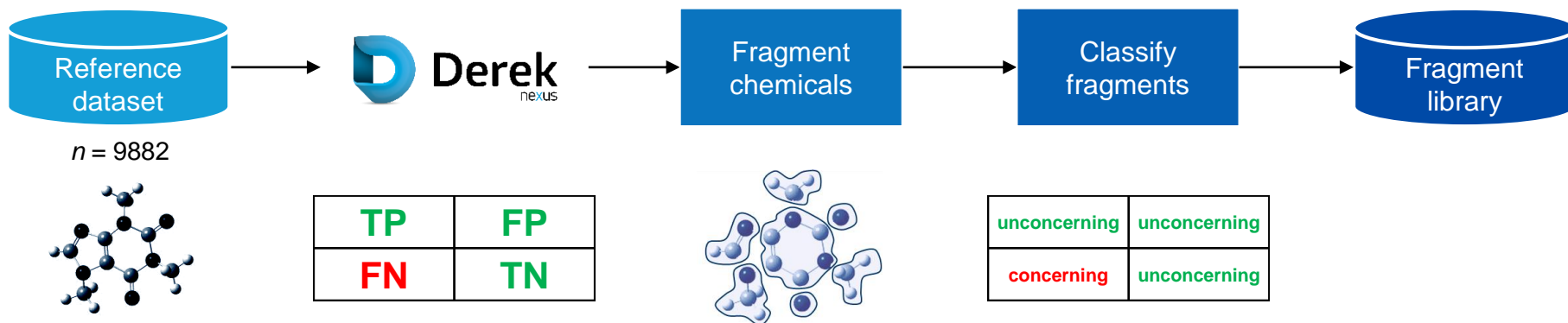


Negative Predictions Workflow in Derek



How does the method work?

Previously performed and stored in Nexus



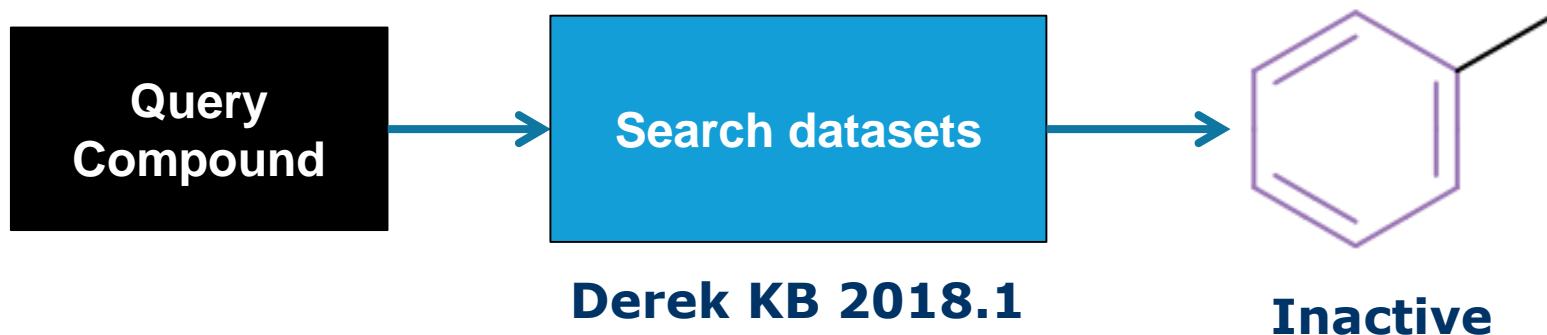
Bacterial Mutagenicity: Lhasa Ames Test Reference Set

- The Lhasa Ames test reference set sources its data from a variety of public data sets.
 - Including ISSSTY, FDA CFSAN and Hansen data sets
- These data sets were curated by Lhasa to remove equivocal, inconclusive or conflicted results.

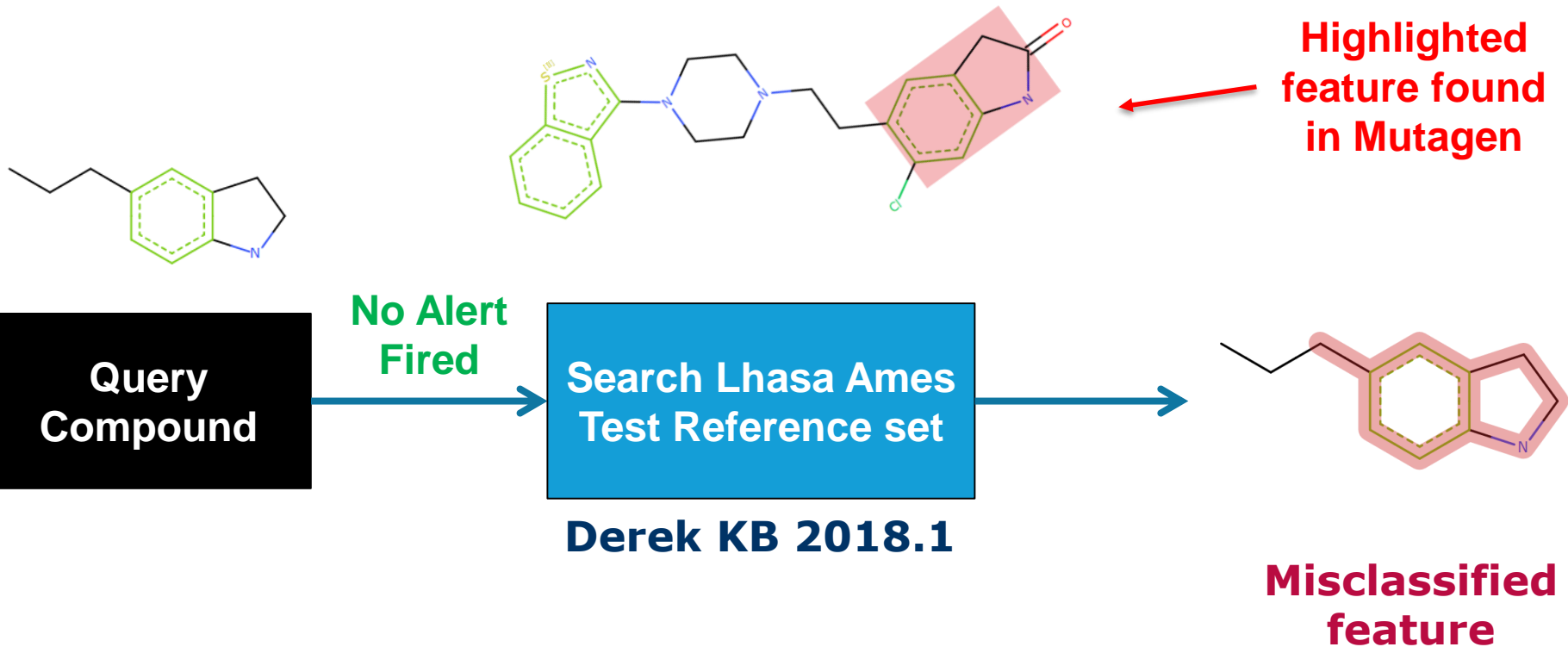
Dataset	Total	Positive	Negative	Equivocal
Lhasa Ames test reference set	9882	4716	5166	0

No misclassified or unclassified features

- This type of prediction is given for compounds where **all features** in the molecule are found in accurately classified compounds from the data sets.

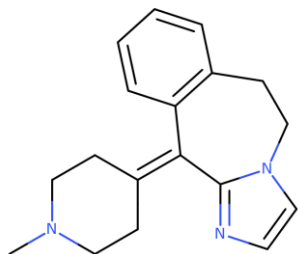


Misclassified features



Expert review: Is highlighted feature the cause of mutagenicity?

Unclassified features: Bacterial Mutagenicity Workflow



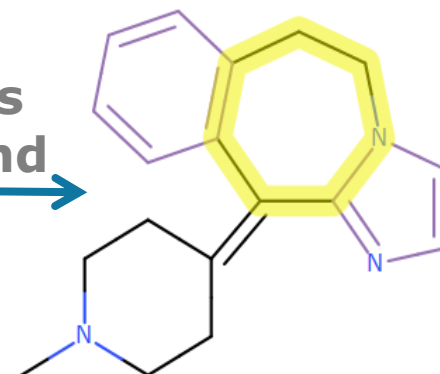
Query
Compound

No Alert
Fired

Search Lhasa Ames
test reference set

Derek KB 2018.1

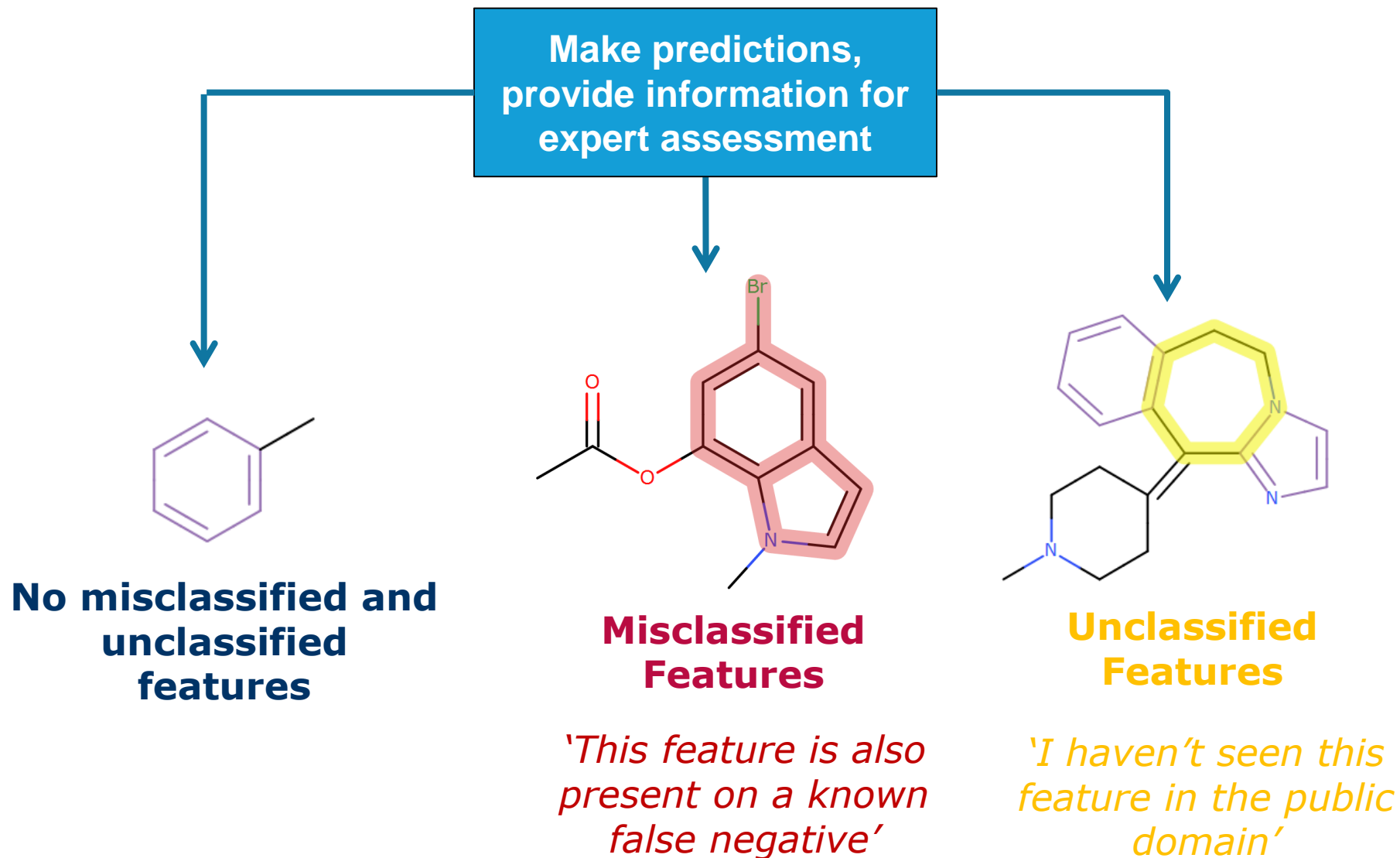
Features
not found



Unclassified
Feature

Expert review: Is highlighted feature the cause for concern?

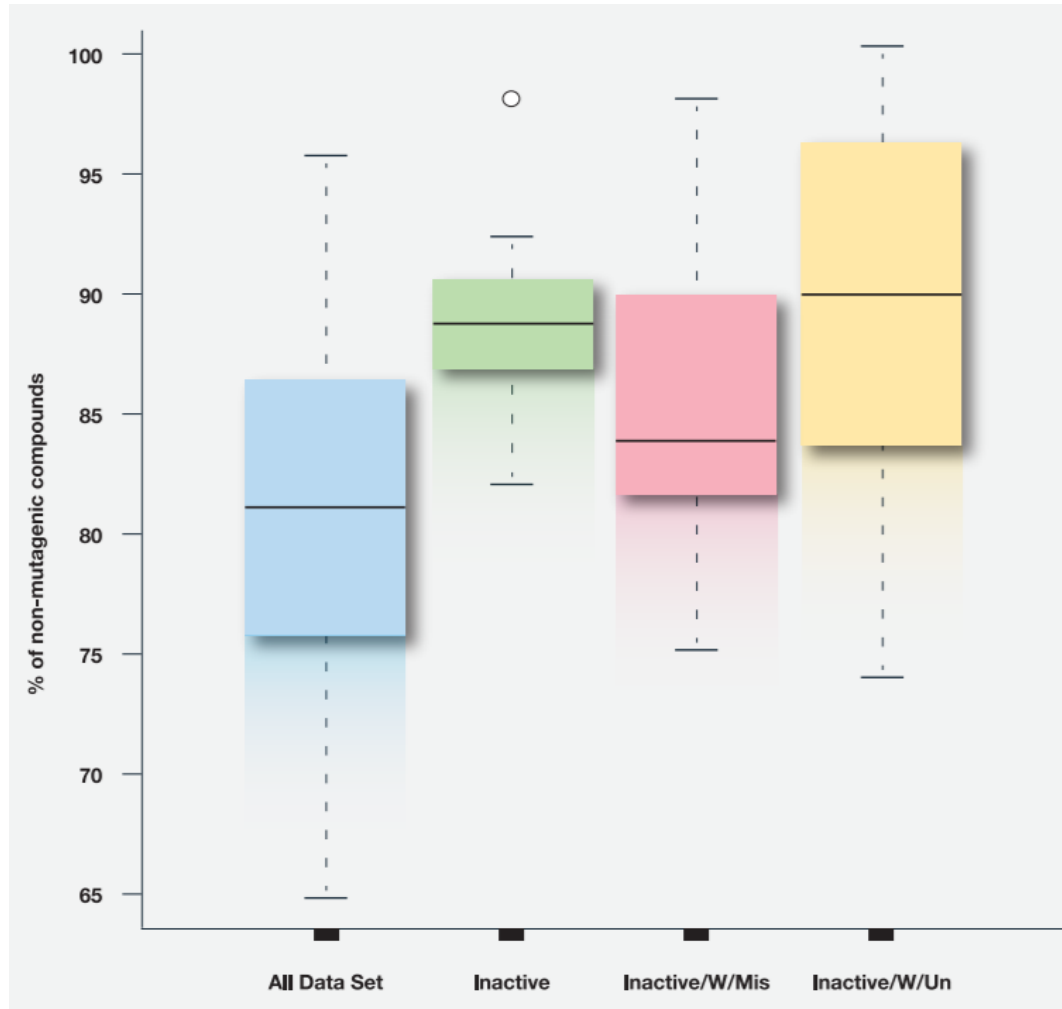
Types of Negative prediction



Negative Prediction Performance - mutagenicity

- The chances of receiving a misclassified or unclassified feature, if an alert has not fired, is approximately 10%
- Analysis using public and proprietary data demonstrates the robustness and accuracy of negative predictions are comparable with the Ames test (~85%)
- The key benefit of this new functionality is it enables further expert assessment, by highlighting features within the query molecule that indicate potential areas for concern or are unknown to the system

Negative Prediction Performance - mutagenicity



References:

<https://www.lhasalimited.org/Public/Library/2017/Negative%20Predictions%20in%20Derek%20WEB%20FINAL.pdf>

Negative Predictions Summary

- The key benefits for negative predictions are:
 - Combines Derek alerts with functionality to generate negative predictions
 - Fits seamlessly into the Derek Nexus user interface and reports
 - Supports expert review and assessment
 - For bacterial mutagenicity *in vitro* there is no “Nothing to Report” or “Out of Domain”

Conclusions

- Derek Nexus is a transparent expert-based toxicity prediction system
- Predictions can be used to meet the ICH M7 guidelines
- Derek Nexus facilitates knowledge extraction from proprietary data leading to improved structural alerts for *in vitro* mutagenicity
- Negative predictions inform the user of any areas of uncertainty to prioritise for expert review

Further Reading

- Importance of data sharing
 - [Scientific Collaborations through Secondments; the Novartis/Lhasa Experience](#)
 - [Mutagenic Impurities: Precompetitive/Competitive Collaborative and Data Sharing Initiatives](#)
- Negative predictions
 - <http://www.lhasalimited.org/products/negative-predictions-for-bacterial-mutagenicity.htm>
 - [It's difficult, but important, to make negative predictions](#)
 - [Establishing best practise in the application of expert review of mutagenicity under ICH M7](#)