ICH M7 – Best Practise in Assessing the Mutagenic Potential of Impurities using *in Silico* Methodologies

Symposium on Streamlining Drug Discovery
31st May 2018, The Shanghai Centre, Shanghai

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Director of Member Services

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Agenda

- About Lhasa
- Background
- *In silico* systems and ICH M7 workflow
- Applying expert review
- Worked Examples

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Introduction to Lhasa Limited

- Established in 1983
- HQ located in Leeds, United Kingdom
- Not-for-profit & Educational Charity
- Facilitate collaborative data sharing projects in the chemistry-related industries
- Controlled by our members
- Creators of knowledge base, statistical and database systems

Derek nexus

Zeneth

Meteor nexus

Sarah nexus

Mirabilis

Vitic

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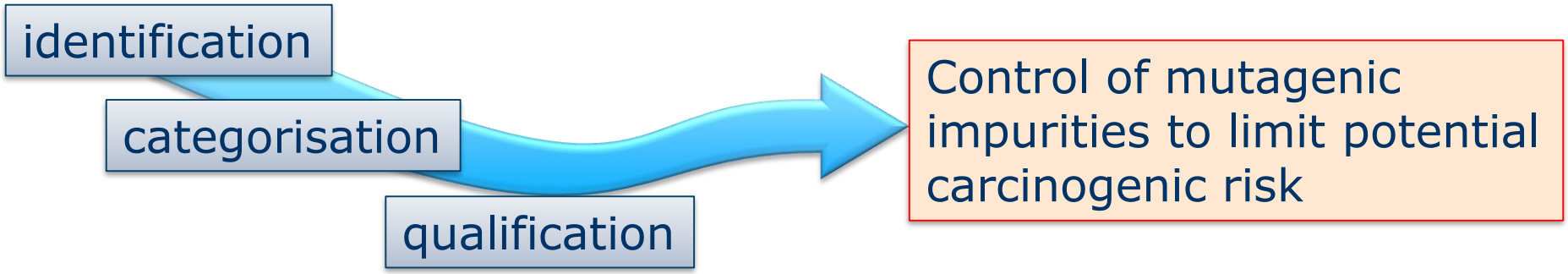
Background

ICH M7

- "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk"
  - 'Global' guidelines – America, Europe and Japan



http://www.ich.org/products/guidelines/multidisciplinary/article/multidisciplinary-guidelines.html

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ICH M7

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*Or other relevant positive mutagenicity data indicative of DNA-reactivity related induction of gene mutations (e.g., positive findings in *in vivo* gene mutation studies)

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ICH M7 – Permits the use of *in silico* predictions

- You may use the Ames (*in vitro*) assay
  - Or use *in silico* predictions in its place
- If you submit *in silico* predictions, you will need:
  - Two predictions – one expert rule-based and one statistical-based
  - To undertake expert review
    - To provide additional evidence for any prediction
    - To support the final conclusion
      - http://www.ich.org/products/guidelines/multidisciplinary/article/multidisciplinary-guidelines.html

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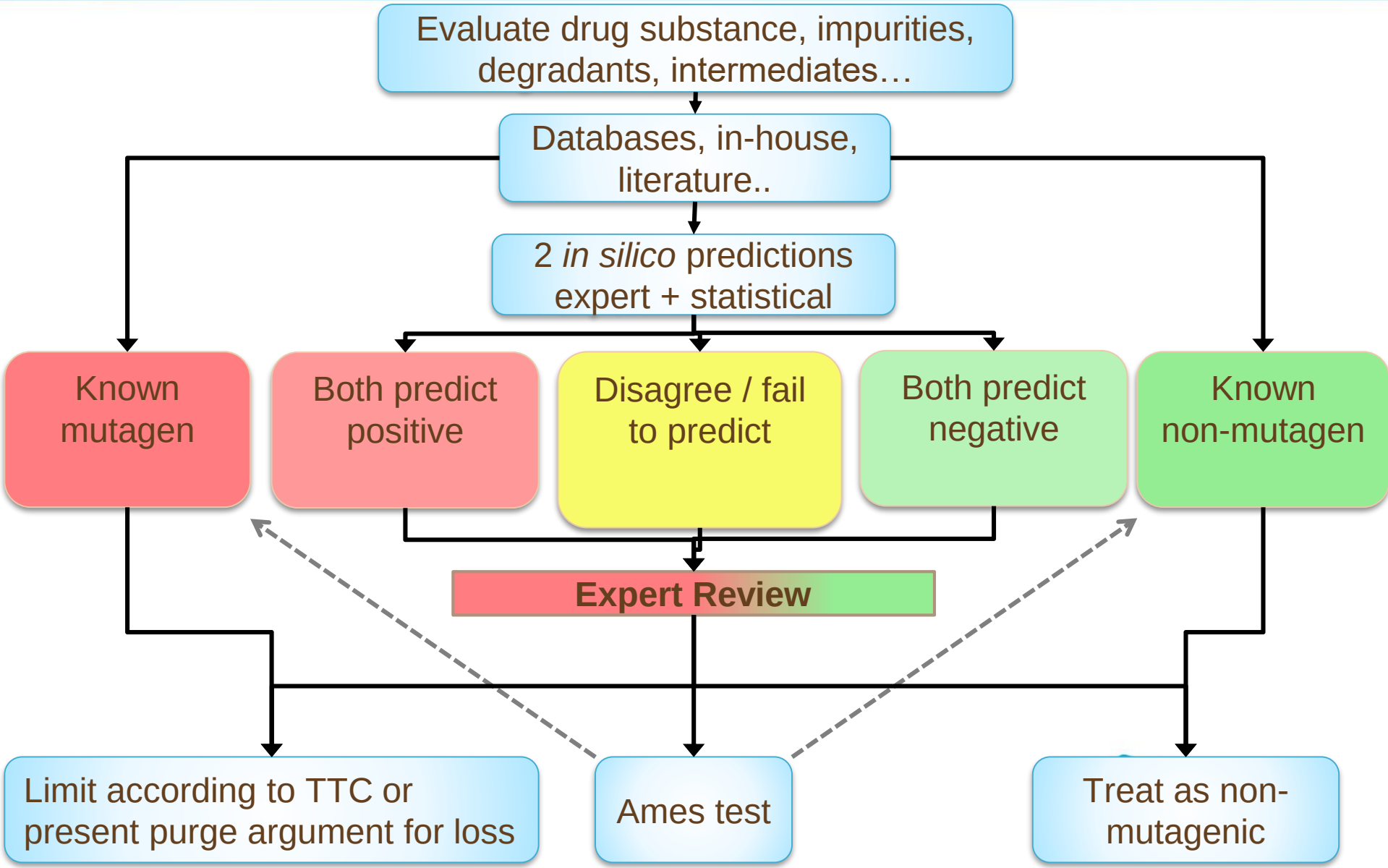
In silico systems and ICH M7 workflow

In silico workflow under ICH M7



Using *in silico* predictions

2 *in silico* predictions
expert + statistical

- "The absence of structural alerts from both is sufficient to conclude that the impurity is of no mutagenic concern"

- Expert review can provide
  - Additional supportive evidence
  - Reason to dismiss an *in silico* prediction
  - Rationale to support the final conclusion

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In silico systems should give you

- A prediction
  - 'Out-of-domain' or 'indeterminate' is **not** a prediction
    - Is there enough information to make an expert call in such cases?
    - Is the scope of the alert/applicability domain clearly defined?
    - How good is the coverage of your chemical space?
- Accuracy
  - You should assess against **your** chemical space (not public data)
- A measure of the model's confidence in a prediction
  - Is it meaningful? Has it been shown to correlate with accuracy
    - It should tell you how much to worry and why

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In silico systems should be

- Regularly updated with new data or knowledge
  - Chemical space is changing – models need to keep up
  - Public vs proprietary chemical space

- Known to regulatory authorities
  - Not essential but expect lots of questions if:
    - They don't understand the approach
    - They have not seen the training data
    - They haven't evaluated the performance
    - They don't get enough supporting data

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In silico systems should give you

- A transparent prediction
- Supporting information (data, explanation)
- The most important criteria
- The ability to defend or challenge every prediction
  - This may be hard if the model automates the conclusion or does not say why
    - A regulator may not accept an automated decision and ask you to explain

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Choosing your *in silico* systems

	Expert	Statistical
☑ Performance	✓	✓
☑ Accuracy	✓	✓
☑ Coverage (out of domain or indeterminate is not a prediction)	✓	✓
☑ Transparent	✓	✓
☑ Explanation of how/why each prediction is made	✓	✓
☑ Clear applicability domain (and methodology for it)	✓	✓
☑ Relevant measure of confidence for each prediction	✓	✓
☑ highlights and explains any uncertainty	✓	✓
☑ Sufficient information to support or challenge a prediction	✓	✓
☑ Can see the underlying data and/or rationale	✓	✓
☑ Robust and broad training set	✓	✓
☑ Curated	✓	✓
☑ Sight of confidential data	✓	✓
☑ Regularly updated	✓	✓
☑ Is used and understood by regulators	✓	✓

Applying Expert Review

ICH M7 says…..

- “If warranted, the outcome of any computer system-based analysis can be reviewed with the use of expert knowledge in order to provide additional supportive evidence on relevance of any positive, negative, conflicting or inconclusive prediction and provide a rationale to support the final conclusion.”
  - http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_Step_4.pdf

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What is Expert Review

Regulatory Toxicology and Pharmacology 73 (2015) 367–377

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

Establishing best practise in the application of expert review of mutagenicity under ICH M7☆

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Regulatory Toxicology and Pharmacology
2015, 73, 367-377

Expert Analysis step-by step

- Enter query compound(s)
- Generate statistical and expert predictions
- Expert review
- (Optionally) source further supporting data
- Report

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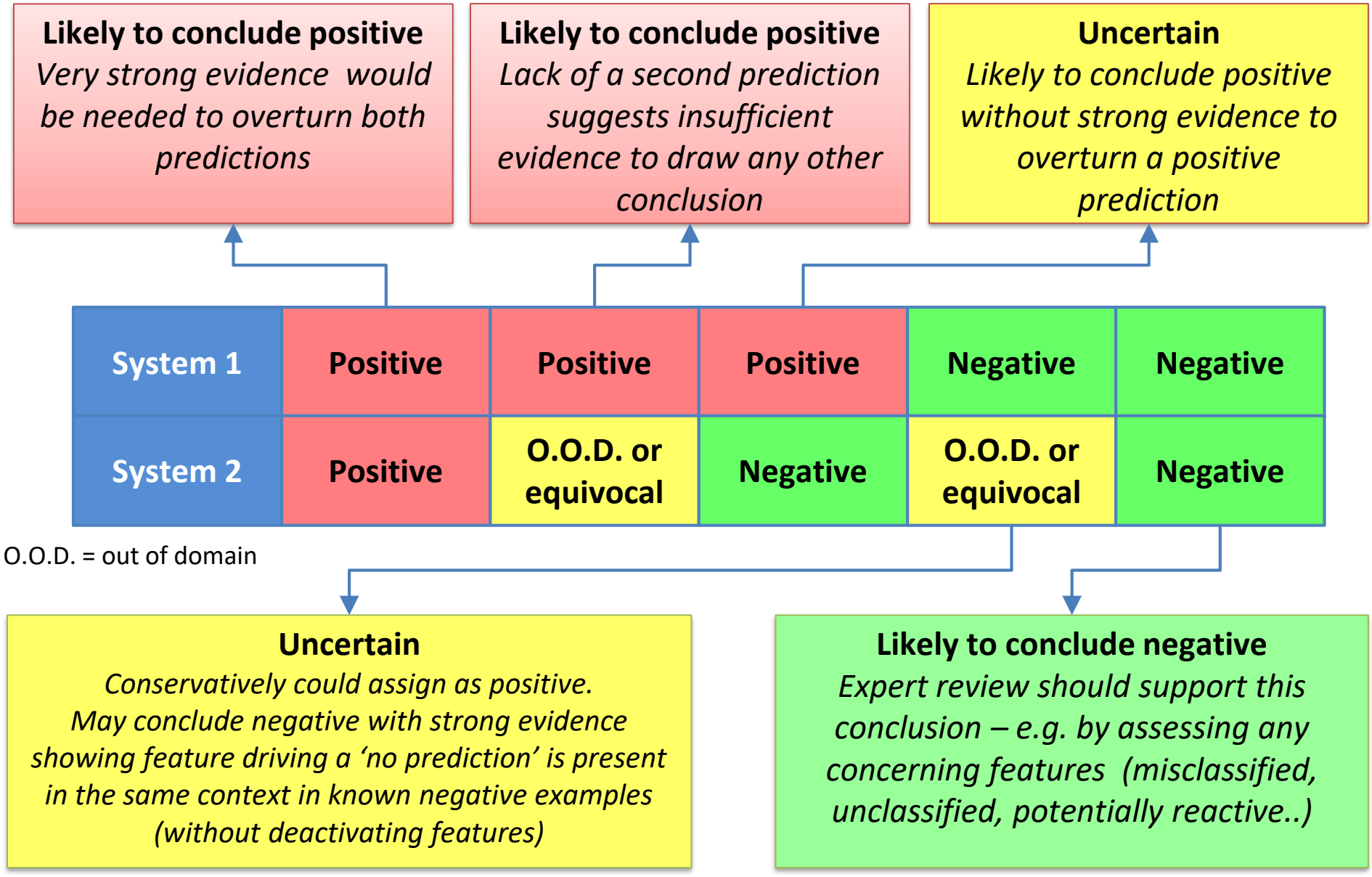

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Dealing with out of domains

- Dealing with Out of Domain (Q)SAR Predictions for ICH M7: A Regulatory and Industrial Perspective
  - Dr. Naomi Kruhlak – FDA
  - Michelle Kenyon – Pfizer
- https://www.lhasalimited.org/publications/dealing-with-out-of-domain-qsar-predictions-for-ich-m7-a-regulatory-and-industrial-perspective/4476

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NME Regulatory Submissions

- Anecdotal evidence suggests new drug applicants routinely encounter a significant number of out of domain results (10% to 50%)
  - Consequence of novel chemistry: Many APIs are out of domain, so highly-similar, late-stage impurities also out of domain
  - Models constructed from public data, represent public chemical space
- Review of new drugs approved in 2016 and 2017 by Dr. Mark Powley, formerly of CDER's Office of New Drugs:

Summary	Count
Approved NMEs with (Q)SAR	18
Approved NMEs with detailed (Q)SAR	13
Total impurities evaluated by (Q)SAR	488
Out of domain results	86

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NME Regulatory Strategies by Applicants

Strategy		Count
Follow up with 3rd model	Apply additional model	5
Comparison with experimentally negative analogue(s)		6
Steric hindrance (based on expert knowledge)	Apply expert knowledge	5
Comparison with (Q)SAR negative analogue		4
Class 4 (positive prediction in presence of unknown fragments)		7
"Class 4-type" conclusions Chemistry covered by experimentally negative API with identical (Q)SAR profile (i.e., negative prediction in 1st model + OOD in 2nd model)		38
Experimental Ames assay	Test/control	12
Control as class 3 impurity – positive prediction in one model		5
Control as class 3 impurity – negative prediction in one model		1
Assign class 5 impurity with no further explanation	Requires follow-up	3
Total		86

OODs – Regulatory conclusions

- OOD results are generated for different reasons by different software
  - Important to have an understanding of why a structure is OOD so it can be handled appropriately
- There are several acceptable strategies for addressing an out of domain
  - An OOD is not a valid prediction and does not contribute to a Class 5 assignment – needs to be followed-up
  - Standard internal practice is to run a 3rd model
  - Using experimental data (and/or predictions) from structural analogues sharing uncovered attributes has been successful
  - Application of expert knowledge can resolve many ambiguous outcomes, including OODs
- Adequate documentation is critical
  - Regulatory (Q)SAR submissions still vary significantly in quality
  - OODs addressed with expert knowledge held to high standard—need a well-documented rationale
  - Inadequately documented submissions may result in additional review cycles

An expert knows…..

- What (s)he needs to know
- How to apply that knowledge
- Where there is uncertainty
- Who to ask for help

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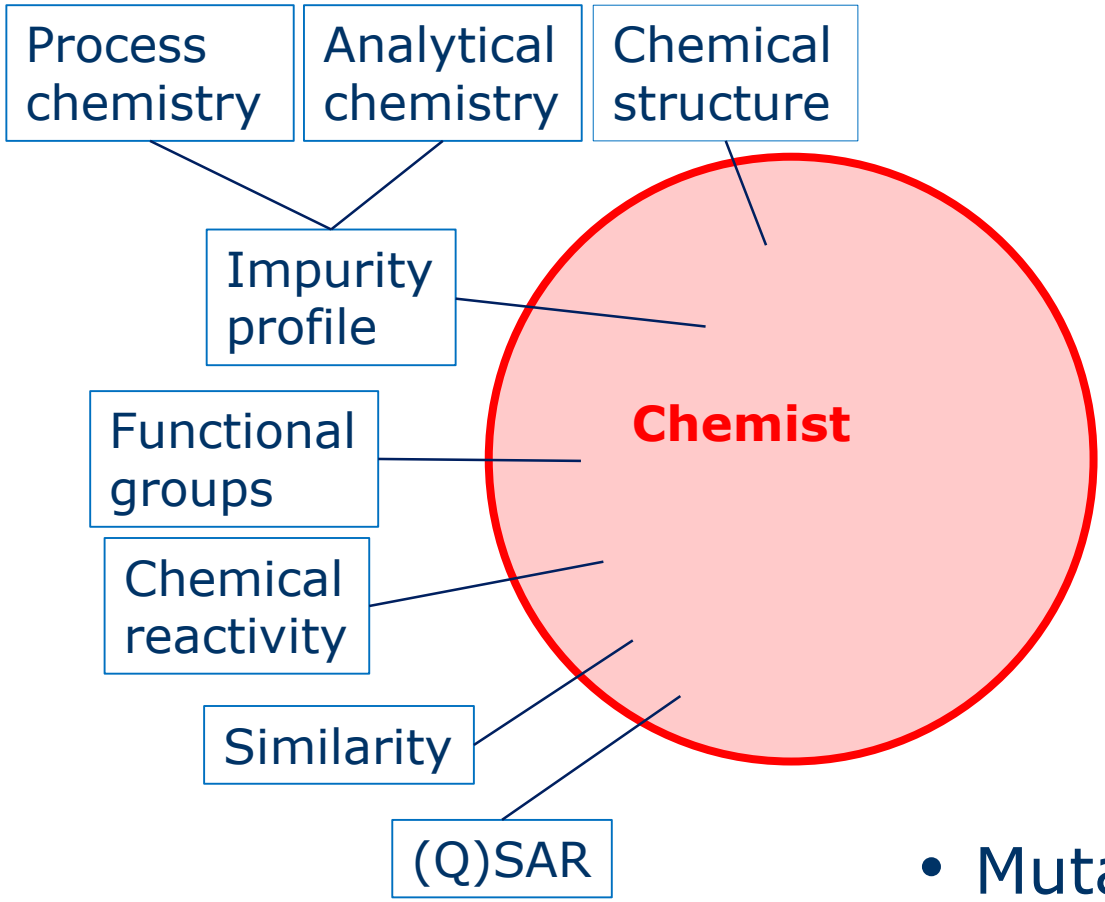
Essential knowledge of an expert (chemistry)



- Mutagenicity is driven by the chemical structure

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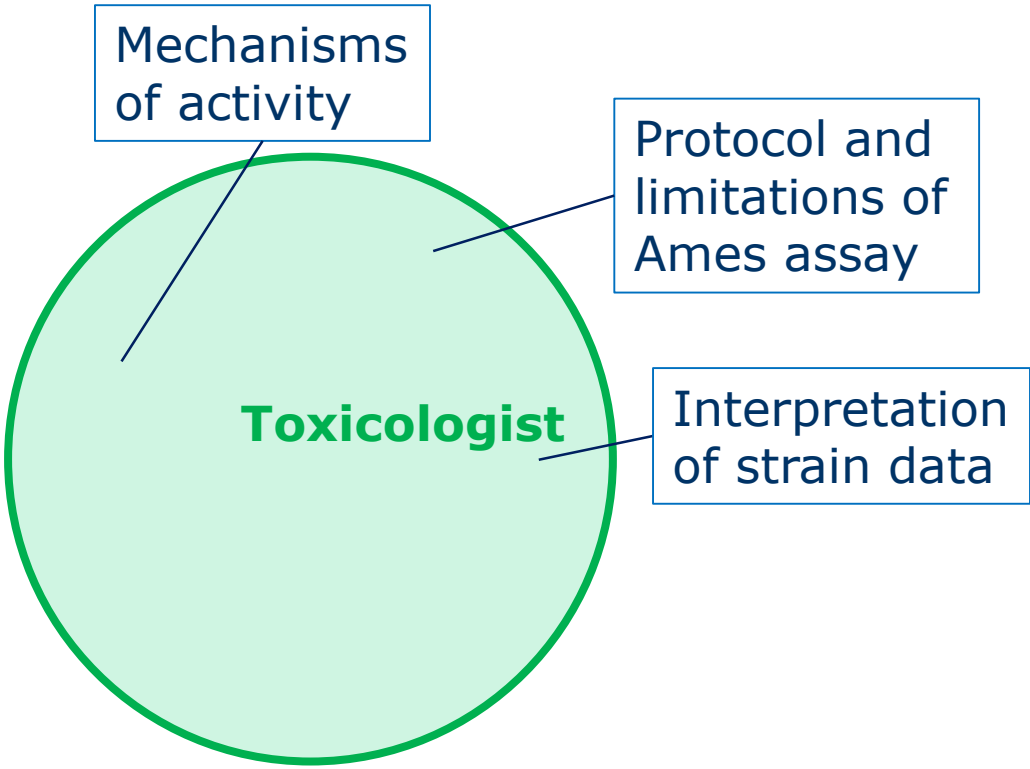
Essential knowledge of an expert (biology/toxicology)



- Mutagenicity is predicted by the Ames assay

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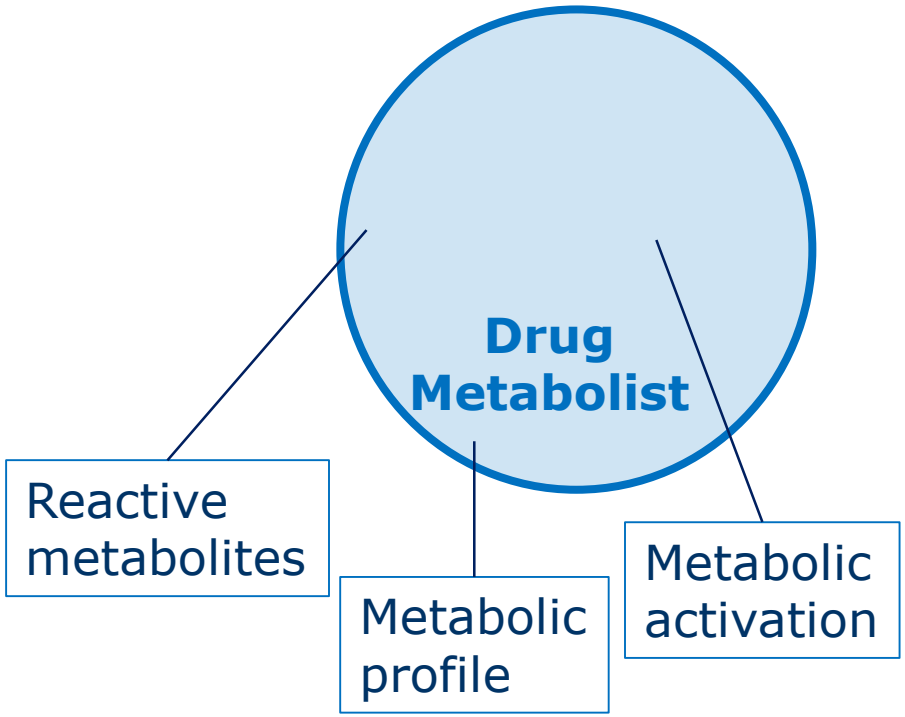
Essential knowledge of an expert (metabolism)

- Many compounds become active through metabolic activation



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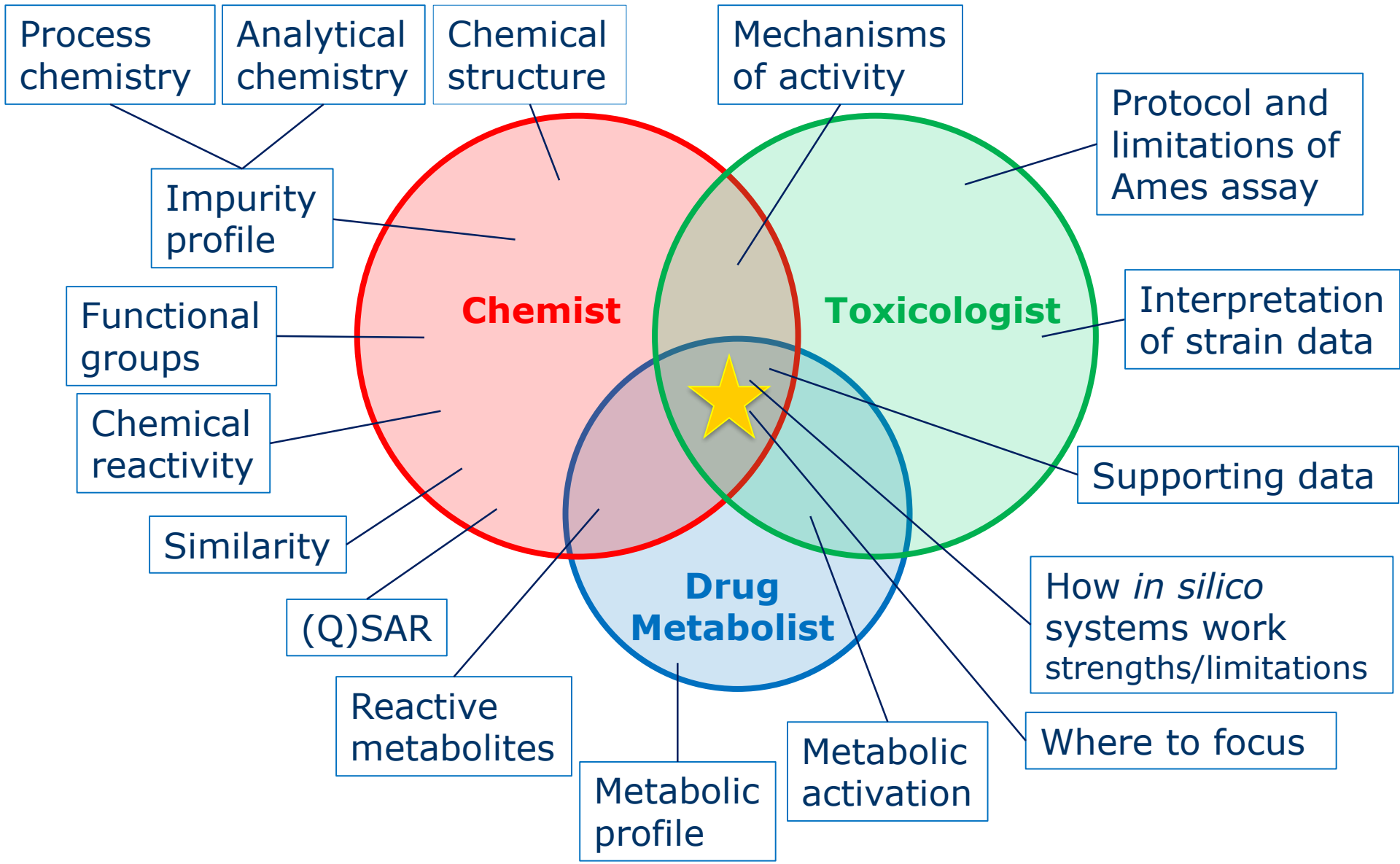
Skills of an expert or an expert team



Skills of an expert or an expert team

- It is unlikely that a single person will be expert in everything
- Many companies have a team that make these assessments

- The choice of software is important
  - It must give you enough information to trust a prediction
  - ....and to challenge it

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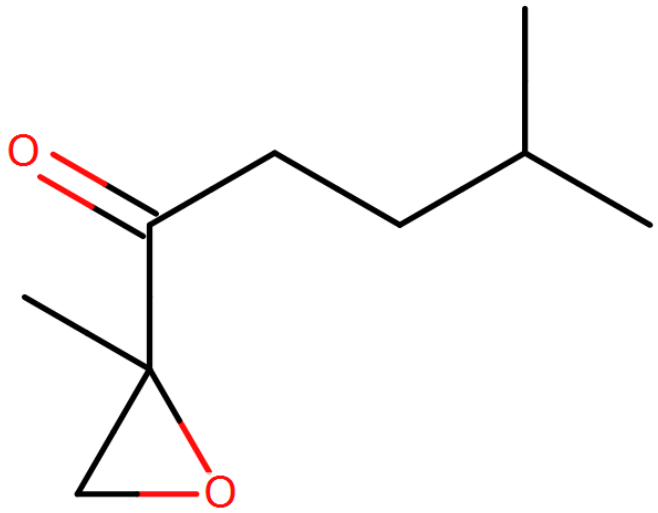
Worked Examples

Example 1



Expert rule-based	**Negative**
Statistical-based	Positive

Conflicting Predictions!

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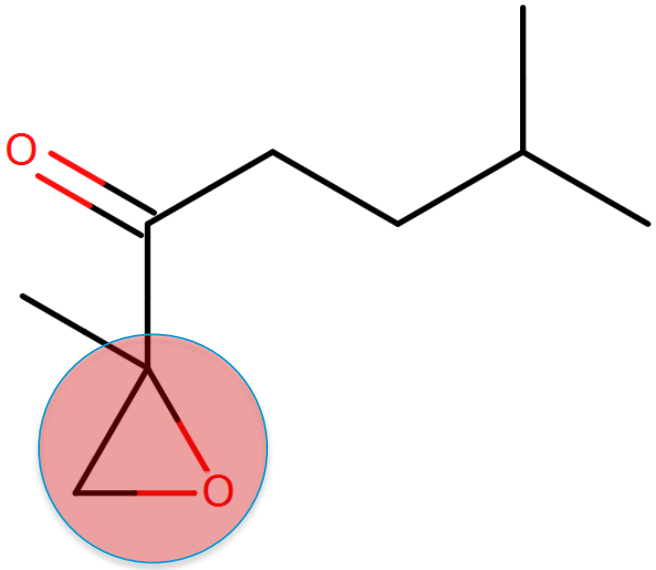
Example 1



Epoxide moiety concerning to the expert system

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The right systems help you with expert review!

- ☑ Performance
  - ☑ Accuracy
  - ☑ Coverage (out of domain or indeterminate is not a prediction)
- ☑ Transparent
  - ☑ Explanation of how/why each prediction is made
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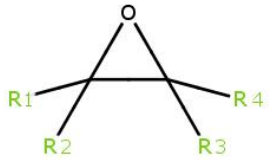
Expert Review – Expert System

- Well supported alert
  - No reason to immediately dismiss the positive prediction



R1-R4 = any atom but with exclusions including glycidyl-type compounds, cyclohexyl epoxides with aliphatic ring fusions, tri- and tetra- alkyl or aryl substituted epoxides, spiroalkyl epoxides, and 1,2-diacid/ester/amide epoxides

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].

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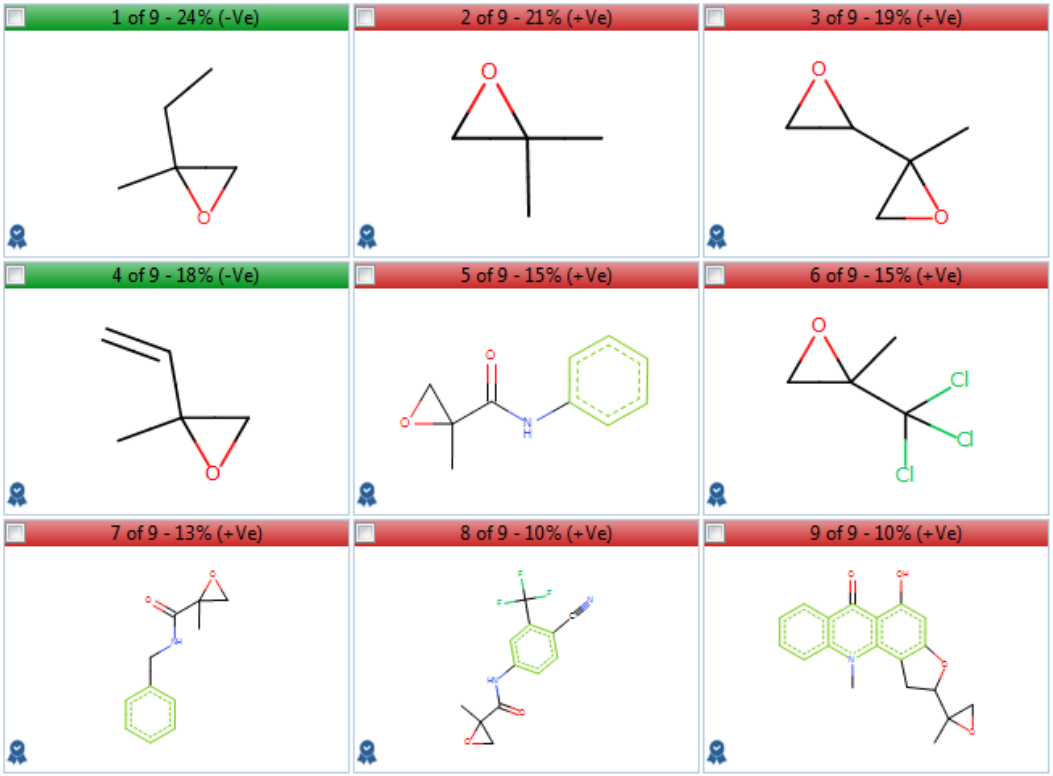
Expert Review – Statistical System

- Overall prediction negative
- But model aware of epoxide moiety
- Close training set examples are positive



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Expert Review Conclusion

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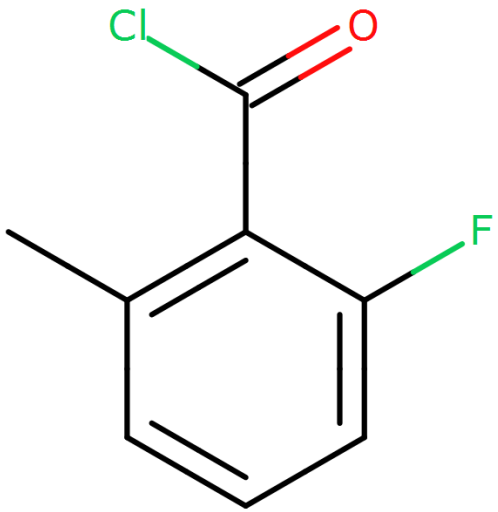
Example 2



Expert rule-based	Equivocal
Statistical-based	Positive (low confidence)

One equivocal and one weakly positive

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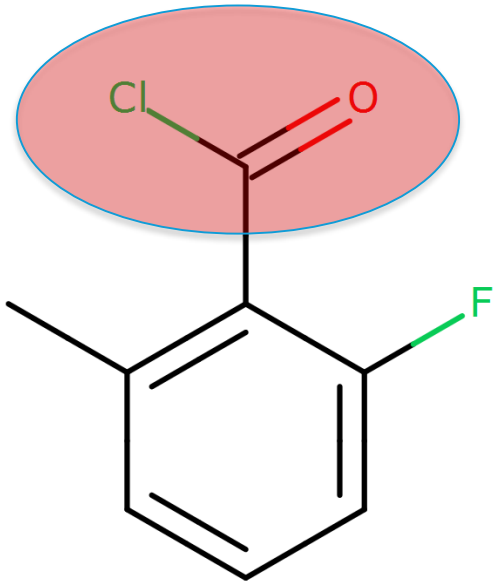
Example 2



Acid chloride moiety concerning

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Expert Review – Expert System

- Positive results are not driven by the acid chloride but by the solvent

This alert describes the activity of carboxylic acid halides, carbamoyl halides, thionyl halides and sulphonyl halides in the Ames test, as illustrated by toxicophores (I), (II) and (III). Testing has generally been restricted to acid chlorides, where positive results are generally observed only when DMSO is used as a solvent, conditions which produce questionable results for these compounds [Amberg et al]. For example, 15/18 compounds that gave positive results under these conditions produced negative results when using solvents other than DMSO, e.g. thionyl chloride and phenacetyl chloride [Amberg et al]. Only 2 compounds were considered to be unambiguous mutagens in this study: dimethylcarbamic chloride, which displayed activity in Salmonella typhimurium TA98 and TA100, and 2-fluorobenzoyl chloride [Amberg et al].

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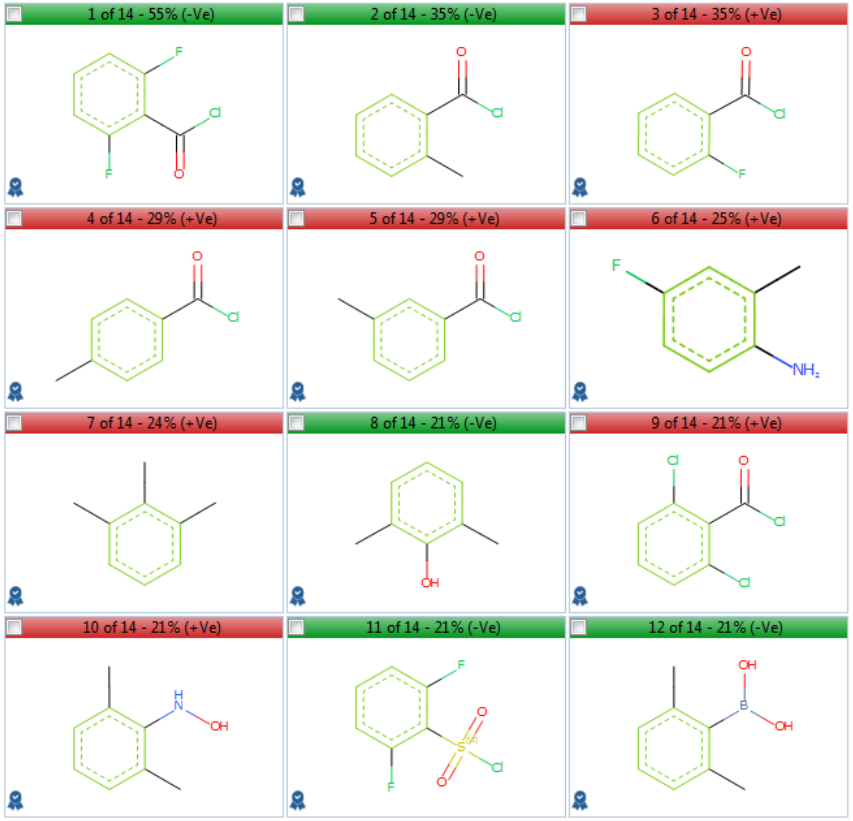
Expert Review – Statistical System

- Weakly positive prediction
- Lack of relevant examples
- Other reasons for activity



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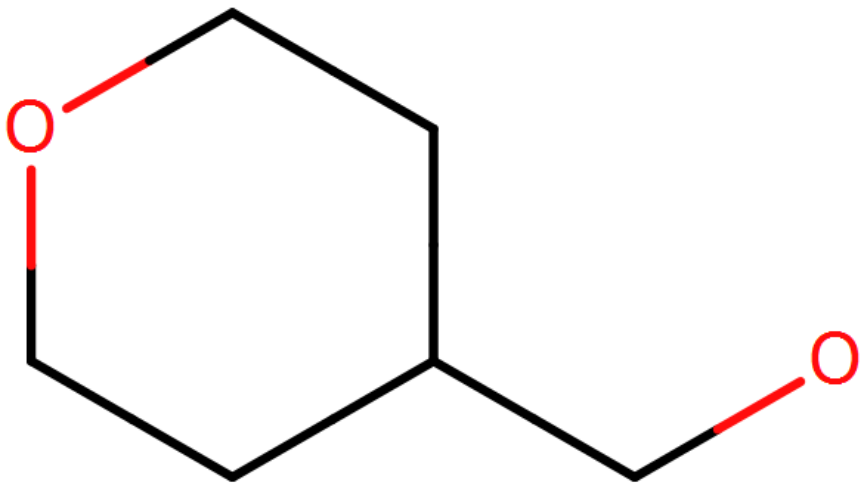
Example 3



Expert rule-based	**Negative**
Statistical-based	Positive

Conflicting Predictions!

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Expert Review – Expert System

- Clear and unambiguous negative prediction

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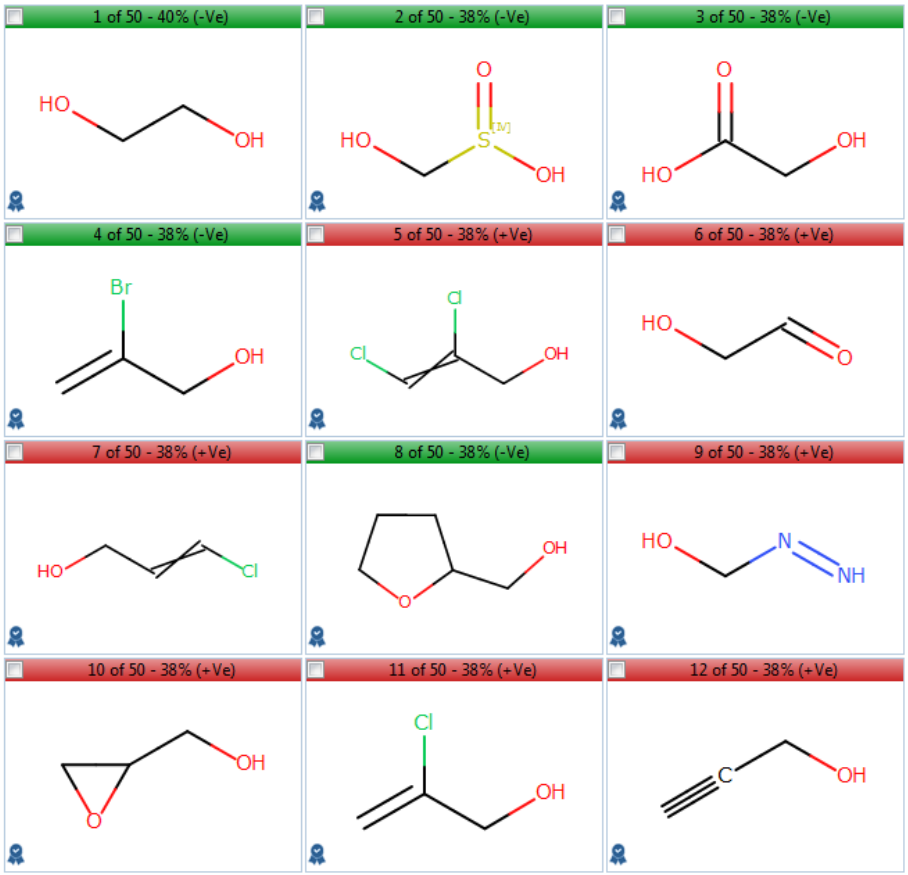
Expert Review – Statistical System

- Positive prediction can be overturned by the expert
- Other reasons for activity or weak positive evidence



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Further reading…..

- Establishing best practise in the application of expert review of mutagenicity under ICH M7.
  - *Regulatory Toxicology and Pharmacology, 2015, 73, 367–377*
- Use of *in silico* systems and expert knowledge for structure-based assessment of potentially mutagenic impurities.
  - *Regulatory Toxicology & Pharmacology,* 2013, *67*, 39–52
- (Q)SAR assessments of potentially mutagenic impurities : A regulatory perspective on the utility of expert knowledge and data submission.
  - *Regulatory Toxicology & Pharmacology,* 2015, *71*, 295–300
- *In Silico* Methods Combined with Expert Knowledge Rule out Mutagenic Potential of Pharmaceutical Impurities: An Industry
  - *Regulatory Toxicology & Pharmacology,* 2012, *62*, 449-55
- A practical application of two in silico systems for identification of potentially mutagenic impurities.
  - *Regulatory Toxicology & Pharmacology,* 2015, *72*, 335-349
- An evaluation of in-house and off-the-shelf in silico models : Implications on guidance for mutagenicity assessment.
  - *Regulatory Toxicology & Pharmacology, 2015, 71, 388-397*

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Acknowledgements

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Questions?