Implementation of ICH M7 Recommended (Q)SAR Analyses

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Society of Toxicology Annual Meeting, Exhibitor-Hosted Session
March 15, 2016

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Overview

- Introduction to (Q)SAR modeling
  - Why is it used for impurities?
  - Underlying principles
  - Modeling methodologies
- How to use (Q)SAR models for impurity assessments
  - ICH M7 language
  - Software acceptability
- Case studies
  - Interpretation of predictions
  - Documentation of analysis
  - Ongoing model enhancement

Drug Impurities

- Why are we concerned with impurities?
  - Unlike API, impurities offer no direct benefit to the patient
  - Impurities will be present regardless of the control strategies applied
  - By their nature, some impurities are reactive and may possess mutagenic potential
  - Mutagenicity is tied to the multi-step process of carcinogenicity
    - Effects will not be evident in patients for many years
    - Defeats the purpose of clinical monitoring

Striking a Balance

- Evaluating the mutagenic potential of drug impurities is an important component of safety assessment
- From a practical standpoint:
  - A cautious approach is warranted but conducting an empirical Ames assay for every potential and known impurity is not feasible or justified

➔ Impurity evaluation process must balance the need for high-throughput with the regulatory imperative of maximizing patient safety

(Q)SAR

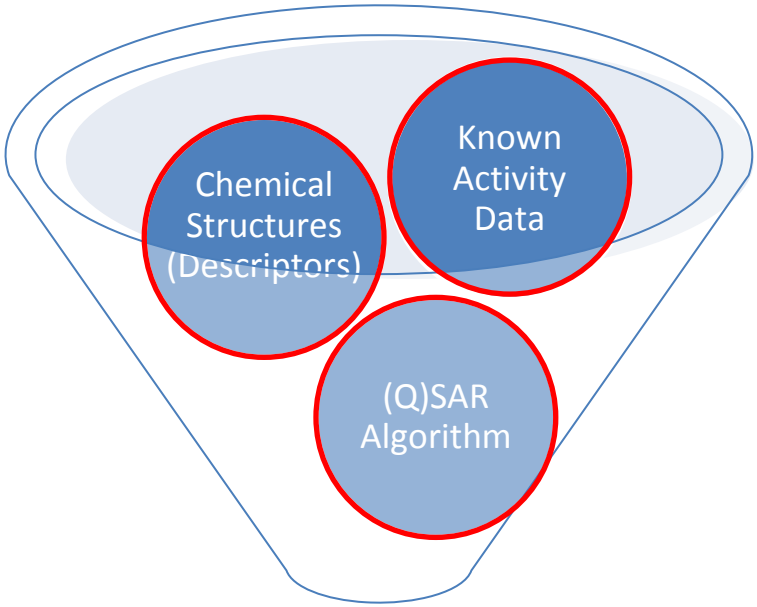
- In silico models provide the high-throughput process needed to handle a large volume of impurities
- Demonstrated to have adequate sensitivity for predicting bacterial mutagenicity (~85% depending on systems used, test sets evaluated, etc.)
  - ✓ Critical for patient safety
- For impurities:
  - Considered “fit for purpose”
  - Recommended by regulatory agencies
  - State-of-the-art approach for assessing mutagenicity

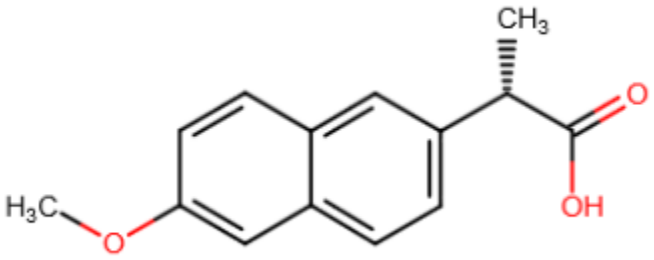
(Q)SAR Modeling: What is it?

- Identifies associations between chemical structural features and biological activity
- Uses the results of actual laboratory testing or clinical outcomes
  - General assumption: Similar molecules exhibit similar physicochemical and biological properties
- Make prediction of a compound's biological activity based on its chemical structure
  - rapidly
  - consistently

QSAR – quantitative – statistically-derived model
SAR – qualitative – expert rule-based model
} (Q)SAR

Building a (Q)SAR Model

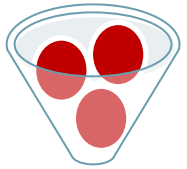




(Q)SAR Model

Activity Prediction

(Q)SAR Methodologies



- Statistically-derived models
  - E.g., partial least squares regression analysis (PLS), support vector machines (SVM), discriminant analysis, k-nearest neighbors (kNN)
  - Use a classic training set
  - Rapid to build
  - Vary in interpretability
- Expert rule-based models
  - Capture human expert-derived correlations
  - Often supported by mechanistic information, citations
  - Highly interpretable
  - Anonymously capture knowledge from proprietary data
  - Time-consuming to build

Why use a computer?

- Why not simply use visual inspection?
  - Highly complex associations can be captured by a model
    - Published alerts are quite general. A model can identify regions within alert space where the alert is less reliable
      - Mitigating features
      - Activity cliffs
  - Consistent, reproducible
  - Rapid – screen multiple chemicals against multiple associations

Chemical Informatics Program

- An applied regulatory research group that:
  - Creates chemical structure-linked toxicological and clinical effect databases
  - Develops rules for quantifying *in vitro*, animal and human endpoint data
  - Evaluates data-mining and (Q)SAR software
  - Develops toxicological and clinical effect prediction models through collaborations with software companies
- Computational toxicology consultations that:
  - Provide (Q)SAR evaluations for drugs, metabolites, contaminants, degradants, etc. to FDA/CDER safety reviewers
  - Perform structure-similarity searching for read-across purposes
  - Provide expert interpretation of (Q)SAR data submitted to FDA/CDER

The ICH M7 Guideline

ASSESSMENT AND CONTR GENIC) IMPURITIES IN PHARMACEUTICALS TO LI C RISK

Section 6:

"A computational toxicolo rmed using (Q)SAR methodologies that predi utagenicity assay (Ref. 6). Two (Q)SAR prediction me each other should be applied. One methodolog nd the second methodology should be st utilizing these prediction methodologies should foll iples set forth by the Organisation for Economi nt (OECD).

The absence of structural y (Q)SAR methodologies (expert rule-based and sta e that the impurity is of no mutagenic concern, and n ed (Class 5 in Table 1)."

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK

M7

Current *Step 4* version

dated 23 June 2014

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

The ICH M7 Guideline

Model output "… 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."

For example:

- Understand the reasoning for a prediction
- Consider data from relevant, structurally similar compounds (analogs) not used to construct model

Expert Knowledge

- Although the use of expert knowledge tends to be subjective, its application can enhance the overall accuracy of predictions by providing a rationale to supersede a positive or a negative prediction and maximize confidence in the overall prediction
- Particularly useful for resolving ambiguous (Q)SAR outcomes (e.g., equivocal, out of domain)

(Q)SAR Software Used by FDA/CDER

- Statistically-Derived Models
  - *CASE Ultra* — MultiCASE, Inc.
  - *Model Applier - Statistical Models* — Leadscope, Inc.
  - *Sarah Nexus* — Lhasa Limited
- Expert Rule-Based Models
  - *Derek Nexus* — Lhasa Limited
  - *Model Applier - Expert Alerts* — Leadscope, Inc.
  - *CASE Ultra - Expert Alerts* — MultiCASE, Inc.

All software above are used by FDA/CDER under Research Collaboration Agreements (RCAs)

CDER (Q)SAR Software Selection Criteria

- Different methodologies can yield different predictions
  - Predictions are complementary
  - Yields higher sensitivity and negative predictivity
- Predictions are chemically meaningful and transparent
  - Structural alerts and associated training set structures can be identified to explain why a prediction was made
  - Application of expert knowledge is facilitated
- Software and models are publicly available
  - Our results are reproducible by pharmaceutical sponsors and others

(Q)SAR Software Acceptability

- Under the ICH M7 guideline, sponsors may submit (Q)SAR analyses performed using models that are fit-for-purpose
  - Commercially available
  - Freely available
  - Constructed in-house
- CDER has prior knowledge of several commercial and freely available (Q)SAR software
- For software that CDER has no prior knowledge, supporting documentation demonstrating that a model is fit-for-purpose is desirable
  - 2 models: expert rule-based and statistical-based
  - Predict bacterial (Ames) mutagenicity
  - Consistent with OECD Validation Principles

OECD Validation Principles

- To facilitate the consideration of a (Q)SAR model for regulatory purposes, it should be associated with the following information:
  1) a defined endpoint
  2) an unambiguous algorithm
  3) a defined domain of applicability
  4) appropriate measures of goodness-of–fit, robustness and predictivity
  5) a mechanistic interpretation, if possible

OECD (2007) Guidance document on the validation of (Quantitative) structure activity-relationship [(Q)SAR] models.

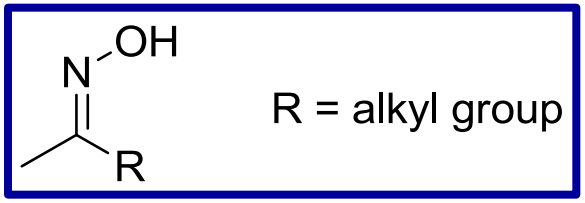
CDER (Q)SAR Consultation Procedure

- For every (Q)SAR analysis:
  1) Check that the impurity structure is correct (*e.g.*, crosscheck with molecular weight and molecular formula)
  2) Check for experimental Ames data
  3) Generate predictions for the impurity structure
     - ➔ Individual model outcomes: positive, negative, equivocal, or out-of-domain
     - ➔ Generate an overall conclusion
  4) Determine the credibility of the reasoning for the predictions, e.g.,
     - identify alerting portion of the molecule, compare to API
     - assess training set structures used to support a prediction
     - evaluate confidence scores
     - confirm structure is within each model's domain of applicability

     Expert Knowledge
  5) Check for experimental data for chemicals with similar structures (analogs)
  6) Report overall expert conclusions

Case Study 1

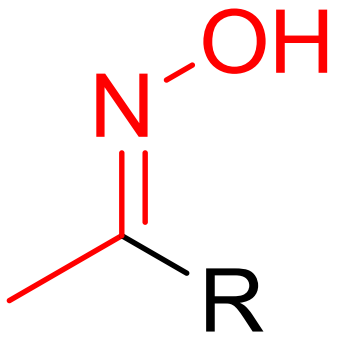
- Chemical structure of the impurity



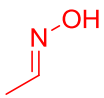
- Predictions from complementary systems:

Software Type	Prediction
Statistical Based	Negative
Expert-rule Based	Equivocal
Overall Software Prediction	Equivocal

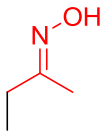
Case Study 1



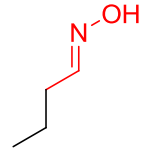
Similar Analogs



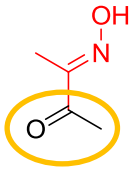
Positive in TA1535 with and without metabolic activation



Positive in TA1535 with and without metabolic activation



Positive in TA1535 with and without metabolic activation



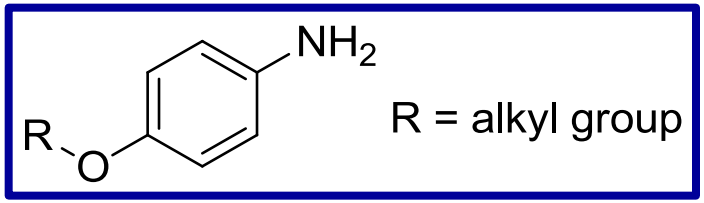
Negative in TA98, TA100, TA1535 and TA1537 with and without metabolic activation

- Expert-rule based prediction is equivocal due to the presence of an oxime/nitrone.
- Nitrones have been shown to be capable of undergoing an intra-molecular hydrogen shift resulting in an electrophilic species capable of undergoing an acylation reaction with DNA (Cronin 2012).
- Structurally similar analogs are mutagenic

➢ Conclusion: Upgraded to positive

Case Study 2

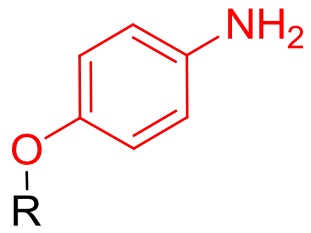
- Chemical structure of the impurity



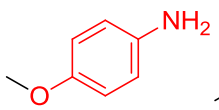
- Predictions from complementary systems (as of September 2015):

Software Type	Prediction
Statistical Based	Equivocal
Expert-rule Based	Negative
Overall Software Prediction	Equivocal

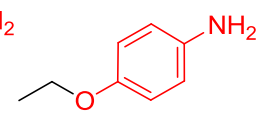
Case Study 2



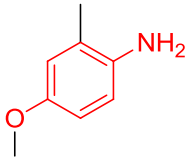
Similar Analogs



Positive in TA100, TA1537 and *E. coli* WP2uvra/pKM101 with and without metabolic activation



Positive in TA100 with metabolic activation



Positive in TA98 and TA100 with metabolic activation

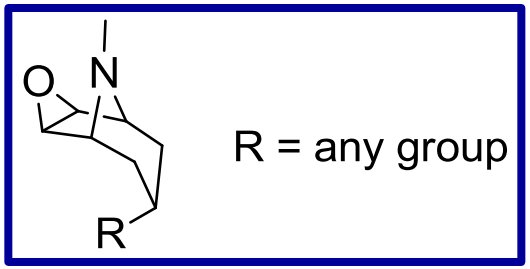
- Statistical based prediction is equivocal due to the presence of a *para*-aminophenoxy group.
- Possible mechanism: the oxy group makes the nitrenium ion more stable due to electron donating property and thus it is more reactive with DNA (Borosky 2007; Ford and Scribner 1981).
- Structurally similar analogs are mutagenic

➢ Conclusion: Upgraded to positive

(Note: expert rule-based system now predicts positive)

Case Study 3

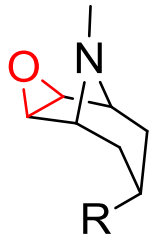
- Chemical structure of the impurity



- Predictions from complementary systems:

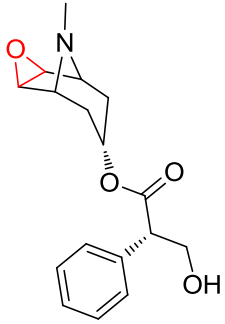
Software Type	Prediction
Statistical Based	Equivocal
Expert-rule Based	Positive
Overall Software Prediction	Positive

Case Study 3



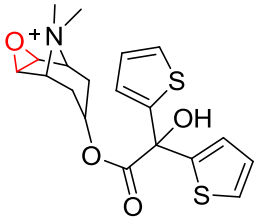
R = alkyl group

Similar Analogs



Scopolamine

Negative in TA97, TA98, TA100, TA1535, TA1537 with and without metabolic activation



Tiotropium

Negative in TA98, TA100, TA1535, TA1537, TA1538 and *E. coli* WP2uvrA with and without metabolic activation

- Statistical based prediction is equivocal and expert rule based is positive due to the presence of an epoxide.
- Epoxides are electrophilic compounds that readily bind to DNA (Citti et al, Sugiura and Goto). Epoxides generally undergo nucleophilic addition by an SN2 mechanism which is highly susceptible to steric influences.
- Structurally similar analogs are non-mutagenic

➢ Conclusion: Downgraded to negative

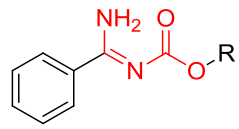
Relevant Information for Reporting

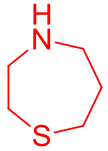
- Materials and methods
  - Name and version of software and (Q)SAR models used
  - Prediction classification criteria, such as the cutoff or threshold values to define a positive/negative/equivocal result
- Results and Conclusions
  - Summary of each prediction, as well as the overall conclusion
  - Confirmation that the impurity is within the model's domain of applicability
  - Description of any confirmatory application of expert knowledge, including analogs (where appropriate) and their sources
  - Rationale for superseding any prediction
- Appendix
  - Raw (Q)SAR outputs
  - Ames data for structurally related compounds used to confirm or refute a prediction

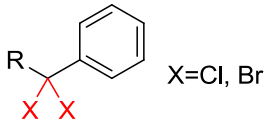
Under-represented Chemicals

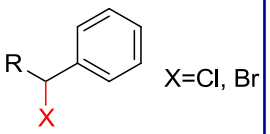
- Bacterial mutagenicity training sets

No Analogs



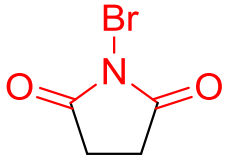


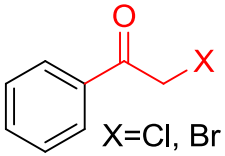


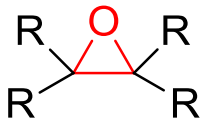


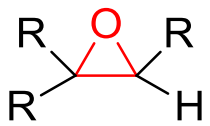
R=any

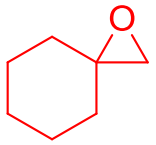
Limited Number of Analogs









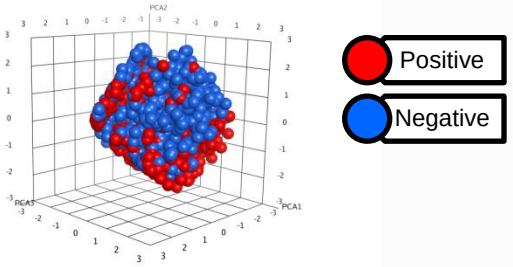


R=any

2016 *Salmonella* Mutagenicity Model

- Identify and address data gaps in current model
  - Clustering Analysis
  - Consultations
  - Selectively add examples from public data sets
- Improve quality of training data
  - Reviewing and resolving conflicting calls
  - Confirming reliability of negative study data
- Improve annotation of data
  - Extract and record strain-specific findings, supporting citations

Distribution of chemical space of the current *Salmonella* mutagenicity training set



Poster Abstract #1400: Kim et al. A Targeted Approach to Improving the Applicability Domain of *Salmonella* Mutagenicity (Q)SAR Models.

Concluding Remarks

- (Q)SAR models provide a high-throughput means to assess mutagenic potential of impurities
  - Models are deemed “fit-for-purpose” under ICH M7
  - At CDER, expert knowledge is routinely applied to (Q)SAR predictions
- Prediction transparency and interpretability are key
  - ICH M7 guideline is not software-specific
  - Choice of software and models impacted by model interpretability
  - Facilitates application of expert knowledge
- Comprehensive reporting reduces the need for follow-up clarification
  - Documentation of software and model names and versions
  - Summary of results and conclusions
  - Additional detail if model predictions are overruled based on expert knowledge

The Chemical Informatics Program Team

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Support:

- Critical Path Initiative
- ORISE
- RCA partners

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17th International Conference on QSAR in Environmental and Health Sciences

www.qsar2016.com

Tuesday June 14th, 2016

	Session 1: Experience from a regulatory accepted use of (Q)SAR models: The ICH M7 guideline for pharmaceutical impurities *Co-chairs: Naomi Kruhlak (US FDA, USA) and Angela White (GlaxoSmithKline, UK)*	**Salon 2B and 2C**
09:00 - 09:40	**Plenary talk - Regulatory use of (Q)SAR in drug development under ICH M7** Mark Powley, US FDA, USA	
09:40 - 10:00	**Incorporating (Q)SAR and expert reviews to ensure compliance with ICH M7** Joel Bercu, Gilead, USA	
10:00 - 10:20	**Practical implementation of QSAR analysis for ICH M7** Jacky Van Gompel, Janssen, Belgium	
10:20 - 10:40	**A targeted approach to enhancing (Q)SAR models for regulatory use** Lidiya Stavitskaya, US FDA, USA	
10:40 - 11:00	**Ames/QSAR international collaborative study** Masamitsu Honma, National Institute of Health Sciences, Japan	
11:00 - 11:20	**Coffee break**	**Salon 2A**
	Session 2: ICH M7 case studies and roundtable *Co-chairs: Naomi Kruhlak (US FDA, USA) and Angela White (GlaxoSmithKline, UK)*	**Salon 2B and 2C**
11:20 - 11:30	**The use of *in silico* tools to support expert review under ICH M7** Alex Cayley, Lhasa Limited, UK	
11:30 - 11:40	**Ease of interpretation vs performance in software applications supporting ICH M7** Suman Chakravarti, MultiCASE Inc., USA	
11:40 - 11:50	**Tools to support regulatory submission of ICH M7 (Q)SAR results** Glenn Myatt, Leadscope Inc., USA	
11:50 - 12:30	**ICH M7 Roundtable Discussion**	