

Dealing with Out of Domain (Q)SAR Predictions for ICH M7: A Regulatory and Industrial Perspective

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Industrial Perspective



WORLDWIDE RESEARCH & DEVELOPMENT



Acknowledgments

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Case Examples

Out of Domains –
Frequency and Impact

Frequency and Impact of Out of Domains

- Frequency
 - 2014: 8%
 - 2015: 9%
 - 2016: 4%
 - 2017: 9%
- Impact
 - Thorough cross-discipline expert reviews if not contained in API
 - Increased time
 - Increase in number of Ames tests
 - To de-risk specific impurities
 - Strategic to increase in silico coverage

Dealing with Out of Domains



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Dealing with Out of Domains

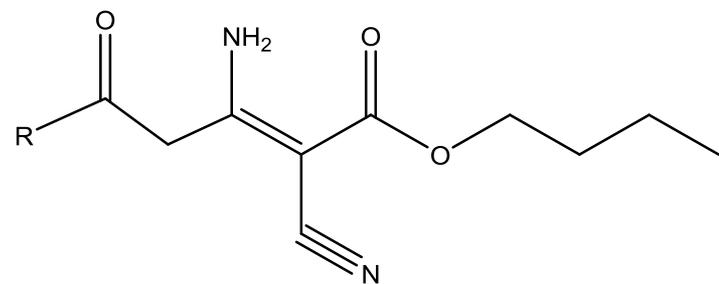
- Is there coverage with proprietary structures?
 - Could a model be built from proprietary structures to add to weight of evidence for a classification?
- What is the chemical reactivity of the compound?
 - Electrophilic?
 - Does it readily form a radical?
 - Is it unstable in an aqueous environment?
 - What is the prediction for the compound(s) expected to form?
- Does another in silico system provide a prediction?

One System Out of Domain

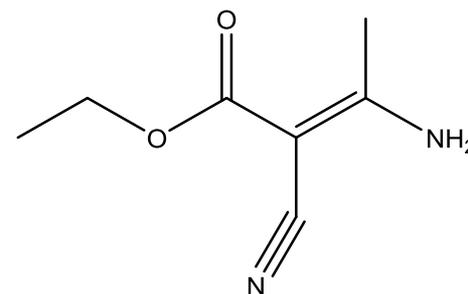
- 2nd system negative
 - Can classify as negative with expert review
 - Structurally similar compounds are not mutagenic
 - Chemical reactivity not expected
- 2nd system positive
 - Generally classified as positive
 - Extensive expert review likely required to justify a negative

Case 1 – OOD + Negative

- Impurity categorized as **Category 5**
 - Derek – **Inactive** with no misclassified or unclassified features
 - Leadscope – **Out of Domain**
 - Additional substituent not contained in parent qualified by negative Ames test on similar substructure
 - Sarah – **Negative** (performed as one regulatory body questioned classification)
 - Still required additional information to support classification



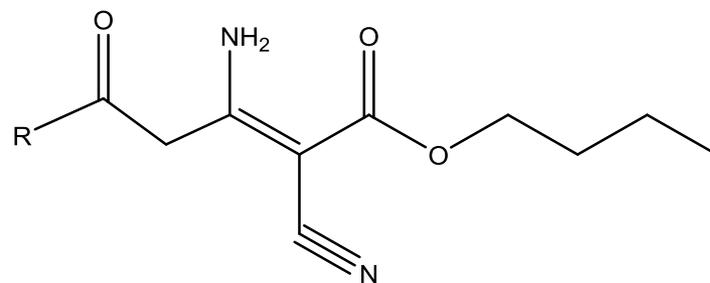
Impurity Structure



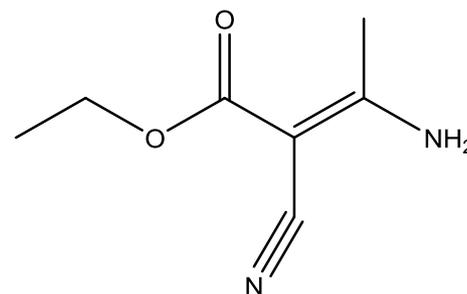
Ames Negative Structure

Case 1 – OOD + Negative (continued)

- Electronics for impurity, Ames negative substructure and Ames positive nitriles compared
- Similar electrophilicity index of impurity and Ames negative substructure support use of substructure to qualify
- Different electrophilicity for Ames positive nitriles
- Quantum mechanical calculations support prediction



Impurity Structure



Ames Negative Structure

Case 2 – OOD + Positive

- Aryl boronic ester impurity
 - Impurity categorized as **Category 3**
 - Derek – **Positive**
 - Sarah – **Out of domain**
 - Note this was 2014 and it now flags as equivocal in Sarah
 - Structurally similar ABAs have been Ames positive

Two Systems Out of Domain

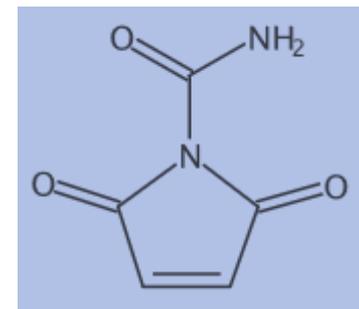
- Related to API?
 - If yes, can it be Class 4?
- If not related to API, is chemical reactivity expected?
 - Yes: Class 3
 - No: Do not classify
 - For early development, there is little risk given higher TTC for short duration treatments
 - For later development, consider the regulatory risk of an out of domain and determine whether Ames testing is warranted
 - Patient population
 - Impurity purge
 - Treatment duration
 - Consider generating data that can be shared with vendors to provide coverage for out of domains in the future

Case 3 – OOD; related to API

- API – Ames **negative**
- API and impurity contain macrocycle
 - Derek – contains **unclassified** feature
 - Sarah – **out of domain**
- API and impurity are structurally related and there were no unique Sarah hypotheses for impurity
 - Categorized as **Class 4-type**

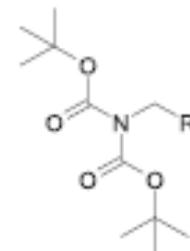
Case 4 – OOD; likely reactive

- Impurity: 2,5-dihydro-2,5-dioxo-1*H*-Pyrrole-1-carboxamide
 - Derek – contains **unclassified** feature
 - Sarah – **out of domain**
- A likely hydrolysis product, 1*H*-Pyrrole-2,5-dione, has been reported mutagenic
 - Based on reactivity and mutagenicity of likely hydrolysis product impurity was classified as **category 3**
 - Impurity tested in TA98 and TA100 (strains reported positive for hydrolysis product) and it was **negative**
- Note – original assessment was in 2015; now inactive in Derek and Positive in Sarah



Case 5 – OOD; reactivity not expected

- Numerous impurities with a bis-boc protection of the amine
 - Derek – contains **unclassified** feature
 - Sarah – **out of domain**
- Bis-boc protection is expected to decrease reactivity of amide
- In each case, the R-group was non-mutagenic or predicted non-mutagenic
- Impurities were not classified
- Teams were informed to consider generating Ames test data as development progressed if above the TTC
 - Several were tested in a 5 strain Ames assay and were negative
 - This data was used to reclassify all as category 5
 - Can create a statistical model using this data to verify classification



Summary: out of domain classification

| (Q)SAR Predictions | Default Prediction | Expert Assessment |
|---------------------------------|--|--|
| One out of domain, one negative | Class 5 | <ul style="list-style-type: none"> No literature evidence of mutagenicity for structure or close analogs No obvious chemical reactivity No alerting features that may be a cause for concern |
| One out of domain, one positive | Class 3 | <ul style="list-style-type: none"> Might be overturned by examining the alert and making argument as to why it is not valid <ul style="list-style-type: none"> e.g. Different chemical environment, or alert derived from training set compounds with other irrelevant structural alerts <u>AND</u> No literature evidence of mutagenicity for structure or close analogs No obvious chemical reactivity No alerting features that may be a cause for concern |
| Two systems out of domain | Out of domain (non-reactive) Or Class 3 (reactive) | <ul style="list-style-type: none"> No literature evidence of mutagenicity for structure or close analogs No obvious chemical reactivity No alerting features that may be a cause for concern Normal control likely possible but Ames test may be required If there is suspect chemical reactivity, classified as class 3 |



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