Machine Learning Enabled “RASAR” Toxicity Models Outperform Animal Test Counterparts

UL Cheminformatics Suite
Model Development: Simple RASAR

- **Jan 2016**: ECHA Database
  - NLP Collection of ECHA C&L
- **Dec 2016**: JHU Publications
  - Skin sens., Eye irrit., Oral models
- **SOT 2016**: REACHAcross Launch
  - https://ulreachacross.com
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Toxic?
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2017  July 2018  Fall 2018

Algorithm Upgrade  Tox Sci Publication  UL Cheminformatics

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2017
Algorithm Upgrade
Data Fusion & Potency

July 2018
Tox Sci Publication
“RASAR” Models

Fall 2018
UL Cheminformatics

Toxic?

Data Fusion

Simple

Toxic?
Data Sources:

Legacy

C&L Inventory

What is the Classification and Labelling Inventory?

This database contains classification and labelling information on notified and registered substances received from manufacturers and importers. It also includes the list of harmonised classifications (Tables 3.1 and 3.2 of Annex VI to the CLP Regulation) and the names of harmonised substances translated in all EU languages.

Companies have provided this information in their C&L notifications or registration dossiers. ECHA maintains the C&L Inventory, but does not review or verify the accuracy of the information.

The number of notifications and substances in the database will

QUESTIONS AND ANSWERS

- Questions and Answers on C&L Inventory
- Q&A on Notification C&L Inventory
- Questions and Answers on Labelling
- Questions and Answers on Classification
- Questions and Answers on Scope and exemptions under CLP
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Production

C&L Inventory

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NTP
National Toxicology Program
U.S. Department of Health and Human Services
Legacy Production

80,908 Chemicals, 74 Properties, 833,844 End-Points
Similarity

Data Source

Similarity

Graph Algorithms

Fingerprinter

Metric

$$M(0100\ldots, 0010) = -\infty \leq x \leq \infty$$

$$x = \frac{|A \cap B|}{|A| + |B| - |A \cap B|}$$

Tanimoto - Heuristic
Data Fusion “RASAR” Model

Acute Oral?

Target

<table>
<thead>
<tr>
<th>Acid</th>
<th>Muta.</th>
<th>Corr.</th>
</tr>
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<tbody>
<tr>
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Data Fusion “RASAR” Model

Target

Acute Oral?

Pos. Source

<table>
<thead>
<tr>
<th>Acid</th>
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<tbody>
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0.4 0.6
Data Fusion “RASAR” Model

Target

Acute Oral?

Hazard & Properties
74 (e.g. H225 - flammable liquid)

Features
74 x 3 = 222 (target, pos, neg)

Database
ECHA C&L, Pubchem, NTP

Learning
Random Forest, Grad. Boost Trees, Multilayer Perceptron

Pos. Source

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Neg. Source

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**Hazard & Properties**
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**Acute Oral?**
- Target: 0.8
- Pos. Source: Acid 0.8, Oral 0.8
- Neg. Source: Acid 0.4, Oral 0.6
Advantages

Familiar Concept
Advantages

Familiar Concept

<table>
<thead>
<tr>
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<th>total</th>
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Endpoint Agnostic

More Data
Advantages

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**More Data**

**Endpoint Agnostic**

**Multi-Task Learning**
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<table>
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<tr>
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<tr>
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<td>406</td>
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<tr>
<td></td>
<td>429</td>
<td>85.5%</td>
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<td>Mutagenicity</td>
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<td>74%</td>
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<td></td>
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## Performance

### Test Performance

Animal Test Reproducibility of 74-92%

Data Fusion RASAR Model balanced accuracies of 84-98% on 100% coverage

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### Table of Simple RASAR and Data Fusion RASAR BAC

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<tr>
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### Cost of Animal Tests

Toxicological “Six Pack” accounted for 55% of all animals used in toxicity testing in EU 2011

$3BB Euro spent on animal tests for toxicology each year

### REACH Registration Case Study

~12,000 and ~13,000 chemicals were received for Phase 1 & 2 registration, respectively

ECHA expects 60,000 registrations in 2018

If we had stopped animal studies for REACH after the 2013 deadline (the data we are using) Using the Data Fusion RASAR would have saved 2.8 million animals

$490 Euro in testing
### Performance and Impact

#### Test Performance

Animal Test Reproducibility of 74-92%

Data Fusion RASAR Model balanced accuracies of 84-98% on 100% coverage

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<td></td>
<td>95%</td>
</tr>
<tr>
<td>Acute Inhalation</td>
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<td>83%</td>
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</tbody>
</table>
## Test Performance

Animal Test Reproducibility of 74-92%

Data Fusion RASAR Model balanced accuracies of 84-98% on 100% coverage

## Cost of Animal Tests

Toxicological “Six Pack” accounted for 55% of all animals used in toxicity testing in EU 2011

$3BB Euro spent on animal tests for toxicology each year

## REACH Registration Case Study

~12,000 and ~13,000 chemicals were received for Phase 1 & 2 registration, respectively

ECHA expects 60,000 registrations in 2018

If we had stopped animal studies for REACH after the 2013 deadline (the data we are using)

Using the Data Fusion RASAR would have saved

- **2.8 million animals**
- **$490 Euro in testing**

1. Study of REACH Registrations was used to extract multiple guideline studies on the same chemical. Conditional pairwise probabilities were calculated to derive accuracy of a repeat experiment.

2. Calculated using leave-one-out cross-validation.

3. Calculated using Five-fold cross-validation results. All chemicals were predicted, i.e. coverage is 100%
Acknowledgements