

## MEETING LOG

**PRODUCT:** Database and Software for Chemical Hazard

**SUBJECT:** Leadscope QSAR Demo

**LOCATION:** CPSC, 5 Research Place, Room 148

**DATE:** 1-29-2020

**ENTRY DATE:** 1-30-2020

**LOG ENTRY SOURCE:** Xinrong Chen

**COMMISSION ATTENDEES:** Xinrong Chen, Michael Babich, Jacqueline Ferrante, Charles Bevington, John Gordon, Kristina Hatlelid, Eric Hooker, Joanna Matheson, Adrienne Layton

**NON-COMMISSION ATTENDEES:** Kevin Cross from Leadscope, Joe Charbonnet from Green Science Policy Institute

**MEETING SUMMARY:** Every attendee introduced themselves and Kevin Cross provided an overview and demonstration of the Leadscope QSAR software tool and database, followed by a group discussion. Slides used by Kevin Cross are attached.

# Leadscope

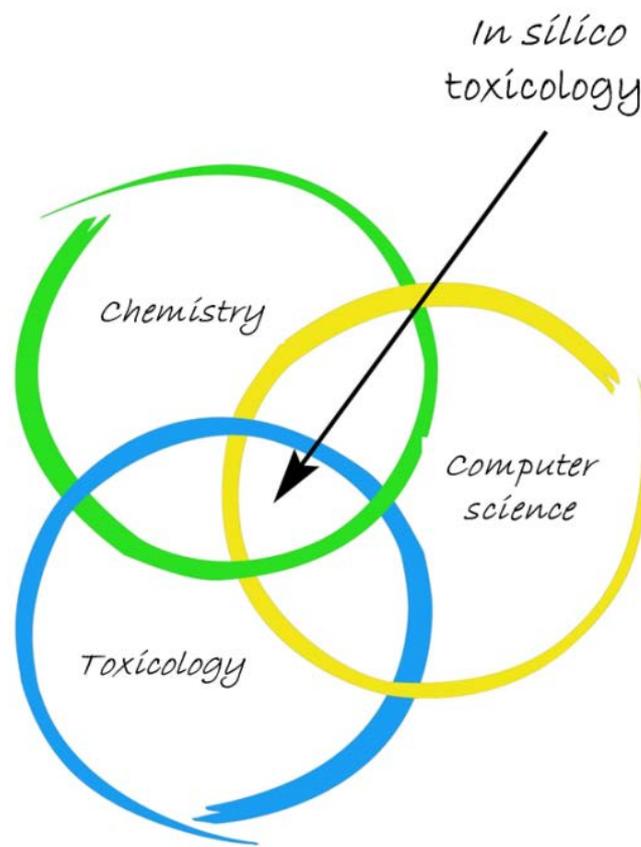


Now part of



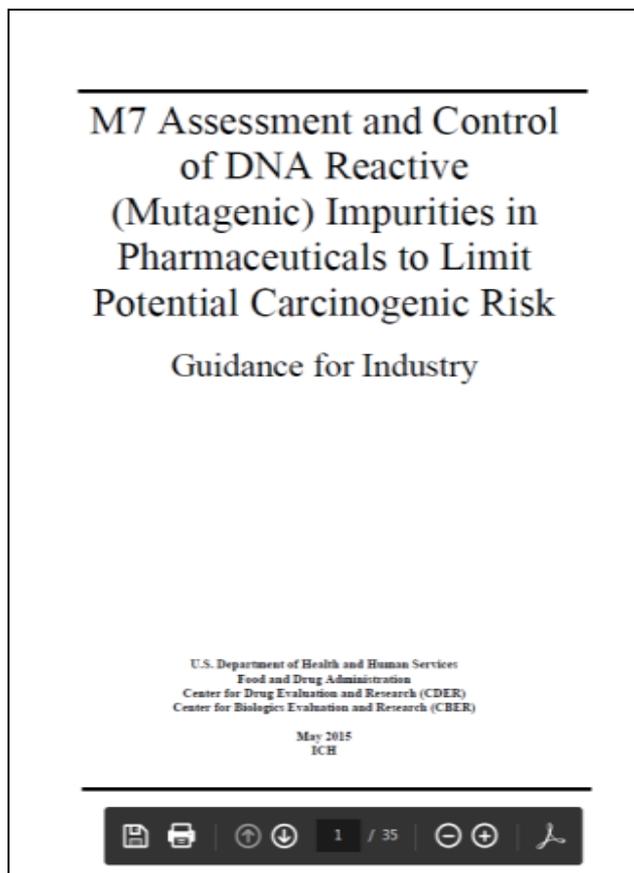
# About Leadscope

- Scientific leader in computational toxicology
- Founded in 1997
- Located in Columbus, Ohio, USA
- Now part of Instem



**AN EXAMPLE OF HOW LEADSCOPE IS  
USED – THE ICH M7 GUIDELINE FOR  
PHARMACEUTICAL IMPURITIES**

# ICH M7 Guideline excerpts



...conducting **database and literature searches** for carcinogenicity and bacterial mutagenicity data...

...an assessment of Structure-Activity Relationships (SAR) that focuses on **bacterial mutagenicity predictions** should be performed...

**Two** (Q)SAR prediction methodologies ... expert rule-based ... statistical-based.

(Q)SAR models utilizing **these prediction methodologies should follow the general validation principles set forth by the Organisation for Economic Co-operation and Development (OECD)**.

The **absence of structural alerts** from two complementary (Q)SAR methodologies (expert rule-based and statistical) **is sufficient** to conclude that the impurity is of no mutagenic concern

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 to provide a rationale to support the final conclusion.

An impurity with a structural alert that is shared (e.g., same structural alert in the same position and chemical environment) with ... related (*negative\**) compounds can be considered as non-mutagenic...

\* Language added

# ICH M7 Guideline and necessary capabilities

...conducting **database and literature searches** for carcinogenicity and bacterial mutagenicity data...

Genetox database

Carcinogenicity database

...an assessment of Structure-Activity Relationships (SAR) that focuses on **bacterial mutagenicity predictions** should be performed...

**Two** (Q)SAR prediction methodologies ... expert rule-based ... statistical-based.

Expert rule-based model

Statistical-based model

(Q)SAR models utilizing these prediction methodologies should follow the general validation principles set forth by the Organisation for Economic Co-operation and Development (OECD).

The **absence of structural alerts** from two complementary (Q)SAR methodologies (expert rule-based and statistical) **is sufficient** to conclude that the impurity is of no mutagenic concern

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 to provide a rationale to support the final conclusion.

Expert review and documentation of results

An impurity with a structural alert that is shared (e.g., same structural alert in the same position and chemical environment) with ... related (*negative\**) compounds can be considered as non-mutagenic...

# Leadscope model applicer

## Complete ICH M7 (Q)SAR

### Implementation

#### Capability

Genetox database

Carcinogenicity database

Expert rule-based model

Statistical-based model

Expert review and  
documentation of results



#### Leadscope products

- Leadscope® SAR genetox database
- Leadscope® SAR carcinogenicity database
- Leadscope® Genetox Expert Alerts
- Leadscope® Statistical QSAR Genetox suite
- Regulatory submission tool

# Supporting publications

Regulatory Toxicology and Pharmacology 77 (2018) 13–24

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

Journal homepage: [www.elsevier.com/locate/yrtph](http://www.elsevier.com/locate/yrtph)

Principles and procedures for implementation of ICH recommended (Q)SAR analyses<sup>a</sup>

Alexander Amberg<sup>a</sup>, Lisa Bellei<sup>b</sup>, Joel Bercu<sup>c</sup>, Dave Bower<sup>d</sup>, Alessa Kevin P. Cross<sup>e</sup>, Laura Custer<sup>f</sup>, Krista Dobo<sup>g</sup>, Eric Dowd<sup>h</sup>, Kevin A. Susanne Glowienke<sup>i</sup>, Jacky Van Gompel<sup>j</sup>, James Harvey<sup>k</sup>, Catrin H. Masamitsu Honma<sup>l</sup>, Robert Jolly<sup>m</sup>, Raymond Kemper<sup>n</sup>, Michelle Kenyon<sup>o</sup>, Naomi Krulhak<sup>p</sup>, Penny Leavitt<sup>q</sup>, Scott Miller<sup>r</sup>, Wolfgang Muster<sup>s</sup>, Andreja Plajer<sup>t</sup>, Mark Powley<sup>u</sup>, Donald P. Quigley<sup>v</sup>, M. Vijayaraj R. Hans-Peter Spirki<sup>w</sup>, Lidya Stavitskaya<sup>x</sup>, Andrew Teasdale<sup>y</sup>, Sandy V. Dennie S. Welch<sup>z</sup>, Angela White<sup>aa</sup>, Joerg Wichard<sup>ab</sup>, Glenn J. Myatt<sup>ac</sup>

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<sup>e</sup> Roche Pharmaceutical Research & Early Development, Pharmaceutical Sciences, Roche Innovation Center, Basel, Switzerland  
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<sup>g</sup> Pfizer, Groton, CT, USA  
<sup>h</sup> Genentech, South San Francisco, USA  
<sup>i</sup> Novartis Institute for Biomedical Research, Basel, Switzerland  
<sup>j</sup> Janssen Pharmaceutica, Beerse, Belgium  
<sup>k</sup> GlaxoSmithKline, Wrexham, UK  
<sup>l</sup> National Institute of Health Sciences, Tsukuba, Japan  
<sup>m</sup> Eli Lilly and Company, Indianapolis, IN, USA  
<sup>n</sup> Novartis, Andover, MA, USA  
<sup>o</sup> FDA Center for Drug Evaluation and Research, Silver Spring, MD, USA  
<sup>p</sup> AbbVie Inc., North Chicago, IL, USA  
<sup>q</sup> KROA, Novato, CA, USA  
<sup>r</sup> Merck Research Laboratories, West Point, PA, USA  
<sup>s</sup> AstraZeneca, Macclesfield, Cheshire, UK  
<sup>t</sup> Amgen, Sunnyvale, CA, USA  
<sup>u</sup> Bayer HealthCare, Berlin, Germany

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Regulatory Toxicology and Pharmacology 102 (2018) 53–64

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Regulatory Toxicology and Pharmacology

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Principles and procedures for handling out-of-domain and indeterminate results as part of ICH M7 recommended (Q)SAR analyses<sup>a</sup>

Alexander Amberg<sup>a</sup>, Roxanne V. Andaya<sup>b</sup>, Lennart T. Anger<sup>c</sup>, Chris Barber<sup>d</sup>, Lisa Bellei<sup>e</sup>, Joel Bercu<sup>f</sup>, Dave Bower<sup>g</sup>, Alessandro Brigo<sup>h</sup>, Zoryanna Cammerer<sup>i</sup>, Kevin P. Cross<sup>j</sup>, Laura Custer<sup>k</sup>, Krista Dobo<sup>l</sup>, Helga Goetsch<sup>m</sup>, Véronique Gervais<sup>n</sup>, Susanne Glowienke<sup>o</sup>, Stephen Gomez<sup>p</sup>, Jacky Van Gompel<sup>q</sup>, James Harvey<sup>r</sup>, Catrin Hasselgren<sup>s</sup>, Masamitsu Honma<sup>t</sup>, Candice Johnson<sup>u</sup>, Robert Jolly<sup>v</sup>, Raymond Kemper<sup>w</sup>, Michelle Kenyon<sup>x</sup>, Naomi Krulhak<sup>y</sup>, Penny Leavitt<sup>z</sup>, Scott Miller<sup>aa</sup>, Wolfgang Muster<sup>ab</sup>, Russell Naven<sup>ac</sup>, John Nicolette<sup>ad</sup>, Alexis Parenty<sup>ae</sup>, Mark Powley<sup>af</sup>, Donald P. Quigley<sup>ag</sup>, M. Vijayaraj Reddy<sup>ah</sup>, Jennifer C. Sauck<sup>ai</sup>, Lidya Stavitskaya<sup>aj</sup>, Andrew Teasdale<sup>ak</sup>, Alejandra Trejo-Martin<sup>al</sup>, Sandy Weiner<sup>am</sup>, Dennie S. Welch<sup>an</sup>, Angela White<sup>ao</sup>, Joerg Wichard<sup>ap</sup>, David Woolley<sup>aq</sup>, Glenn J. Myatt<sup>ar</sup>

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<sup>e</sup> Global, Foster City, CA, USA  
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<sup>j</sup> Novartis Institute for Biomedical Research, Basel, Switzerland  
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<sup>l</sup> GlaxoSmithKline, Wrexham, UK  
<sup>m</sup> National Institute of Health Sciences, Tsukuba, Japan  
<sup>n</sup> Eli Lilly and Company, Indianapolis, IN, USA  
<sup>o</sup> Novartis, Andover, MA, USA  
<sup>p</sup> FDA Center for Drug Evaluation and Research, Silver Spring, MD, USA  
<sup>q</sup> AbbVie Inc., North Chicago, IL, USA  
<sup>r</sup> KROA, Novato, CA, USA  
<sup>s</sup> Merck Research Laboratories, West Point, PA, USA  
<sup>t</sup> AstraZeneca, Macclesfield, Cheshire, UK  
<sup>u</sup> Amgen, Sunnyvale, CA, USA  
<sup>v</sup> Bayer HealthCare, Berlin, Germany

ABSTRACT

The International Council for Harmonisation (ICH) M7 guideline describes a hazard assessment process for impurities that have the potential to be present in a drug substance or drug product. In the absence of adequate experimental hazard data, (Q)SAR analysis may be used as a test to predict impurity (DNA reactive (mutagenic)) potential. However, in certain situations, (Q)SAR software is unable to generate a positive or negative prediction either because of conflicting

<sup>a</sup> FDA/CDER Declaration: The findings and conclusions in this manuscript have not been formally reviewed by the FDA and should not be construed as representing any agency determination or policy. The mention of commercial products, their names, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services.

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 E-mail address: [joerg@leadscope.com](mailto:joerg@leadscope.com) (G.J. Myatt).

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Regulatory Toxicology and Pharmacology

Journal homepage: [www.elsevier.com/locate/yrtph](http://www.elsevier.com/locate/yrtph)

Extending (Q)SARs to incorporate proprietary knowledge for regulatory purposes: A case study using aromatic amine mutagenicity<sup>a</sup>

Ernst Ahlberg<sup>a</sup>, Alexander Amberg<sup>b</sup>, Lisa D. Bellei<sup>c</sup>, David Bower<sup>d</sup>, Kevin P. Cross<sup>e</sup>, Laura Custer<sup>f</sup>, Kevin A. Ford<sup>g</sup>, Jacky Van Gompel<sup>h</sup>, James Harvey<sup>i</sup>, Masamitsu Honma<sup>j</sup>, Robert Jolly<sup>k</sup>, Elisabeth Joossens<sup>l</sup>, Raymond A. Kemper<sup>m</sup>, Michelle Kenyon<sup>n</sup>, Naomi Krulhak<sup>o</sup>, Lara Rahnke<sup>p</sup>, Penny Leavitt<sup>q</sup>, Russell Naven<sup>r</sup>, Claire Neelan<sup>s,t</sup>, Donald P. Quigley<sup>u</sup>, Dana Shuey<sup>v</sup>, Hans-Peter Spirki<sup>w</sup>, Lidya Stavitskaya<sup>x</sup>, Andrew Teasdale<sup>y</sup>, Angela White<sup>z</sup>, Joerg Wichard<sup>aa</sup>, Craig Zwacki<sup>ab</sup>, Glenn J. Myatt<sup>ac</sup>

Combines public and proprietary information to help understand SAR around primary aromatic amines

Fig. 1. Selection matrix analysis. Showing the extending and identifying of new additional points.

Metagenesis, 2018, XX, 1–16  
 doi:10.1002/mtagen.yrtph020  
 Original Manuscript

OXFORD

Original Manuscript

Extending (Q)SARs to incorporate proprietary knowledge for regulatory purposes: is aromatic N-oxide a structural alert for predicting DNA-reactive mutagenicity?<sup>a</sup>

Combines public and proprietary information to help understand SAR around aromatic N-oxides

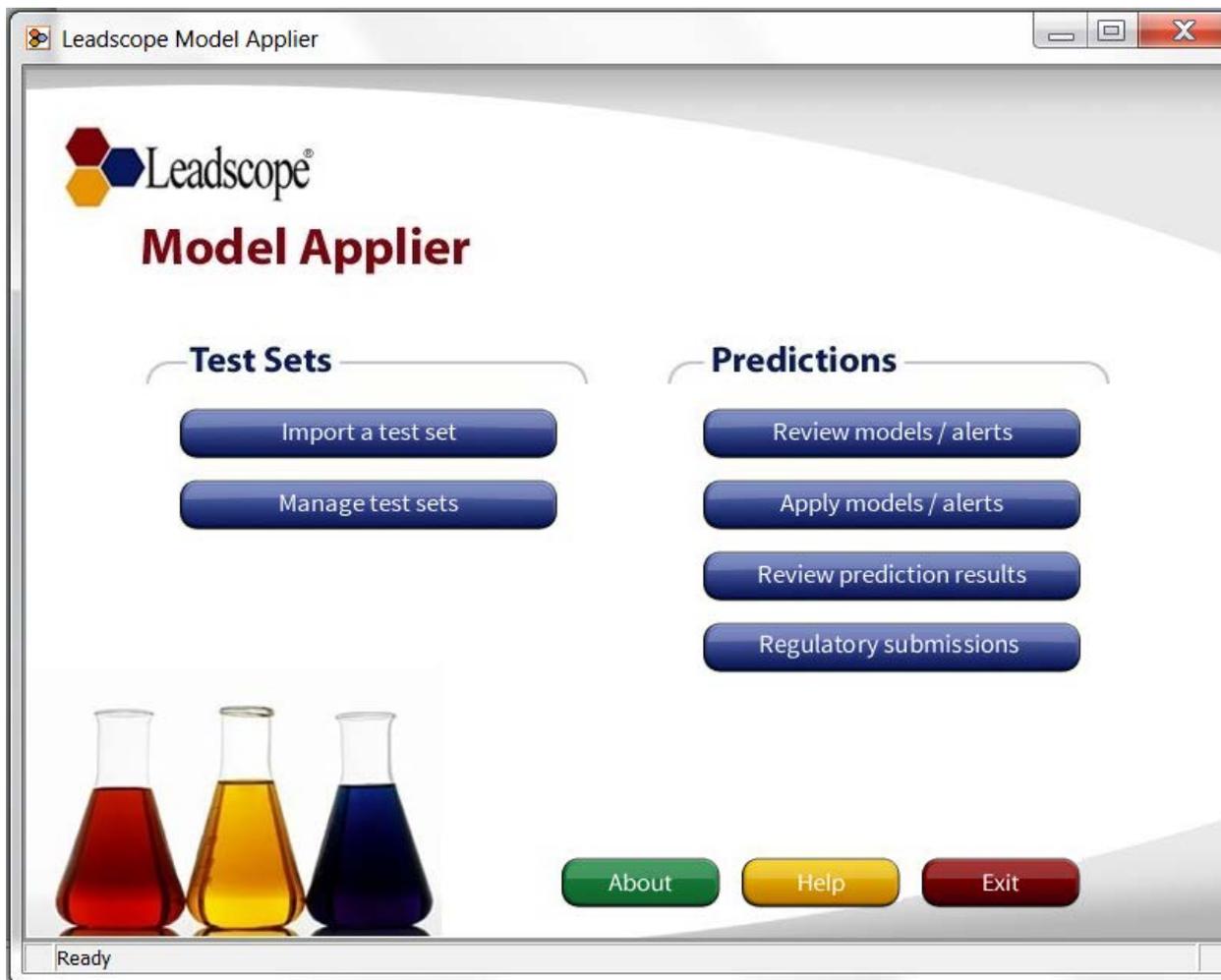
Public examples with no other alerts

Proprietary examples

14 positive proprietary examples

Respective proprietary examples

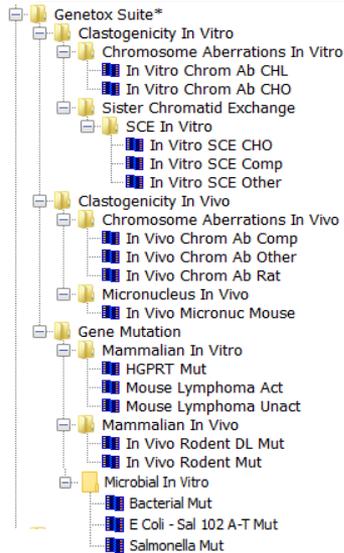
# Leadscope model applier demo



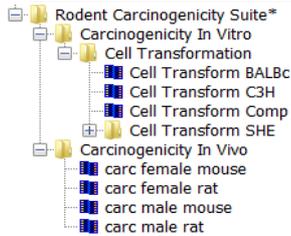
# **LEADSCOPE PRODUCTS AND TECHNOLOGY**

# Leadscope QSAR models

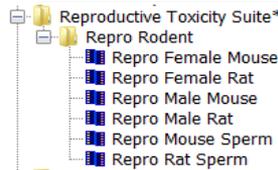
## Genetic toxicity



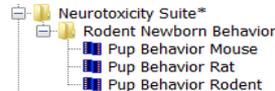
## Carinogenicity



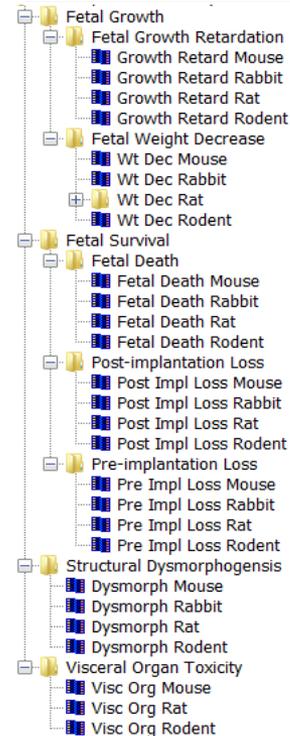
## Reproductive



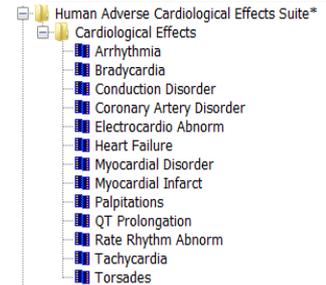
## Neurotoxicity



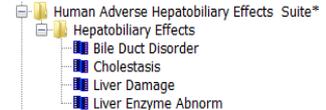
## Developmental



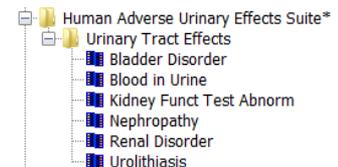
## Cardiological



## Hepatobiliary



## Urinary tract



# New statistical and expert alert models

- **Acute toxicity**
  - Predicts Globally Harmonized System (GHS) categories
  - Uses statistical models and expert alerts
- **Skin sensitization**
  - Predicts the results of the Local Lymph Node Assay
  - ECETOC categories of extreme/strong, moderate, weak and non-sensitizers were used
- **Ecotoxicity**
  - Predicts the GHS ecotoxicity classifications
  - Predicts Acute Algae; Acute Crustacean, and Acute Fish, including Bluegill, Fathead Minnow, and Rainbow Trout

Apply Statistical Models / Expert Alerts

Prediction Results

Summary: Acute Toxicity

Prediction Calls when applying selected models to test set: LS-10-1

Structure	Invertebrate Acute Consensus	Rainbow Trout Acute Categorical Consensus	Algae Acute Consensus	Minnow Acute Consensus	Blue Gill Acute Categorical Consensus
<chem>Oc1ccccc1</chem>	GHS Category III	GHS Category III	GHS Category III	GHS Category III	GHS Category III

LS-10-1

Find Analogs... Explain... Generate Full Reports Compare Consensus With Data... Save All Results

Back Next Finish Cancel

Apply Statistical Models / Expert Alerts

Prediction Results

Summary: Skin Sensitization

Prediction Calls when applying selected models to test set: LS-1427-1

Structure	LNA Categorical Consensus	High model v1 Experimental Positive	High model v1 QSAR-only Prediction	Moderate model Run #3 v1 Experimental	Moderate model Run #3 v1 QSAR-only	Weak model Run #4 v1 Experimental	Weak model Run #4 v1 QSAR-only
<chem>CC1=CC=CC=C1</chem>	Weak	Negative	Not to Assess	Negative	Negative	Positive	Positive

LS-1427-1

Find Analogs... Explain... Generate Full Reports Compare Consensus With Data... Save All Results

1 row selected

Back Next Finish Cancel

Apply Statistical Models / Expert Alerts

Prediction Results

Summary: Ecotoxicity

Prediction Calls when applying selected models to test set: LS-10-1

Structure	Invertebrate Acute Consensus	Rainbow Trout Acute Categorical Consensus	Algae Acute Consensus	Minnow Acute Consensus	Blue Gill Acute Categorical Consensus
<chem>Oc1ccccc1</chem>	GHS Category III	GHS Category III	GHS Category III	GHS Category III	GHS Category III

LS-10-1

Find Analogs... Explain... Generate Full Reports Compare Consensus With Data... Save All Results

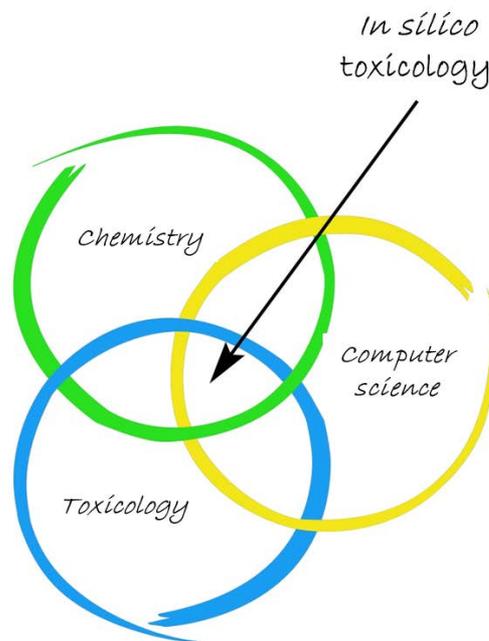
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# Leadscope Databases

<b>Leadscope Toxicity Database</b>	Over 190,000 chemical records with over 400,000 toxicity studies from literature sources, including <ul style="list-style-type: none"><li>- acute and repeated dose toxicity studies</li><li>- reproductive and developmental toxicity studies</li><li>- skin &amp; eye sensitivity and irritation</li></ul>
<b>SAR Carcinogenicity Database</b>	High quality carcinogenicity database, includes 3,596 compounds with 11,538 test results
<b>SAR Genetox Database</b>	High quality genetic toxicity database, includes over 11,500 compounds with more than 184,200 test results

# Extract knowledge from public and proprietary data

- Read-across
- Chemical/biological data mining
- Build models
- Find alerts



# Flexible deployment and reporting options



Personal



Hosted



Enterprise



Web-based



Web services and  
Knime plug-ins



**Thank you!**