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

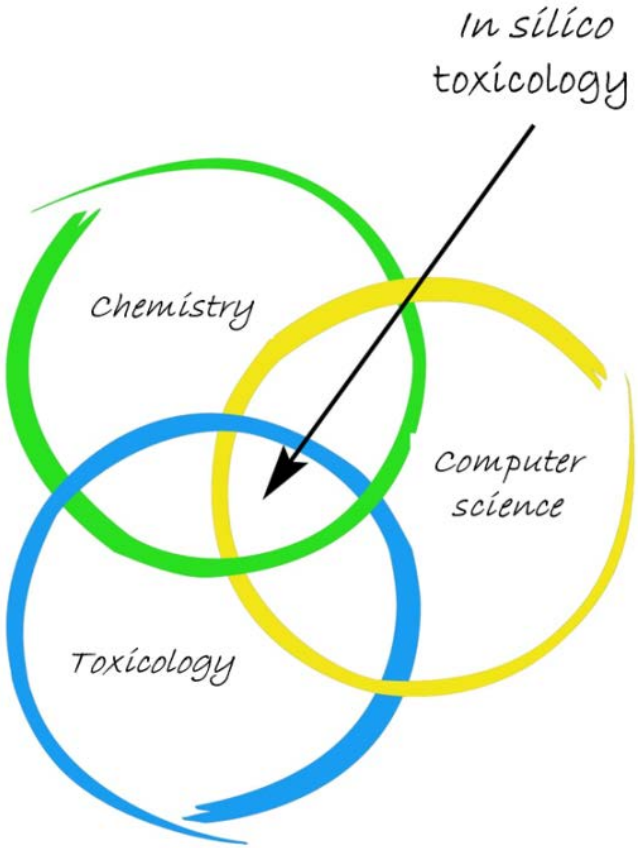
MEETING SUMMARY: Every attendee introduced themselves and Kevin Cross provided an overview and demonstration of the Leadscope QSAR software tool and database, followed by a group discussion. Slides used by Kevin Cross are attached.

Leadscope

Now part of

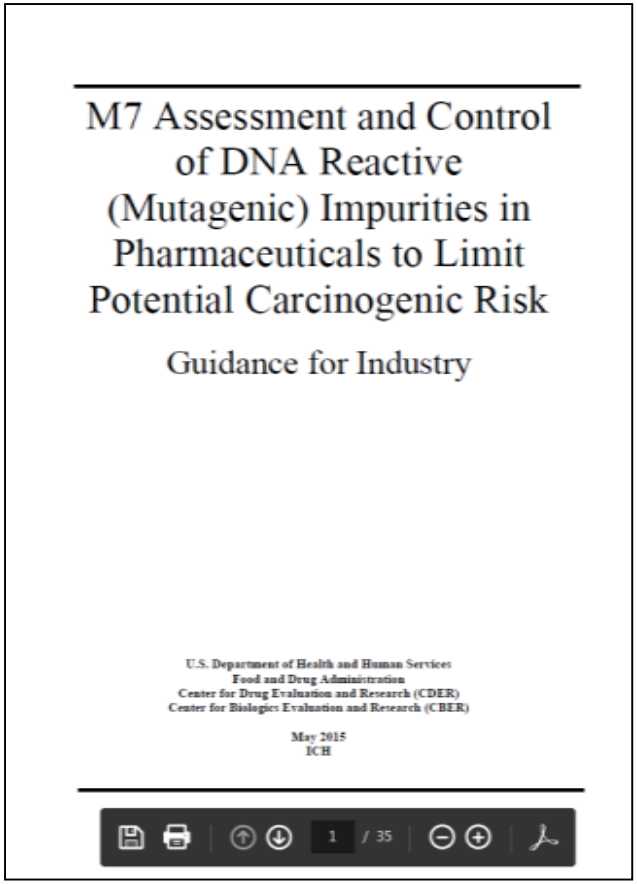
About Leadscope

- 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


M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2015
ICH

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…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.

(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).

- Expert rule-based model
- Statistical-based model

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

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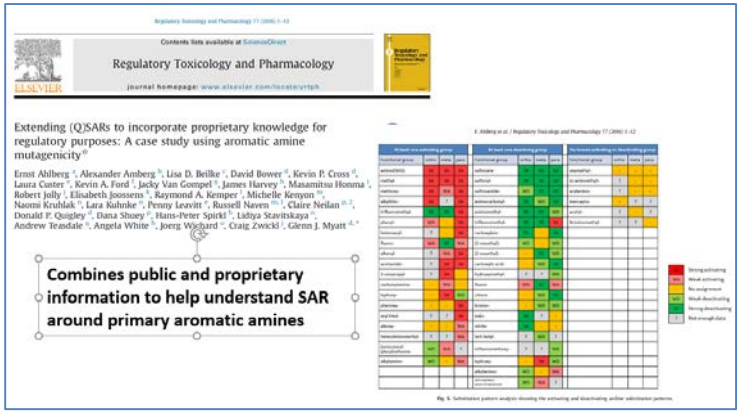
- Expert review and documentation of results

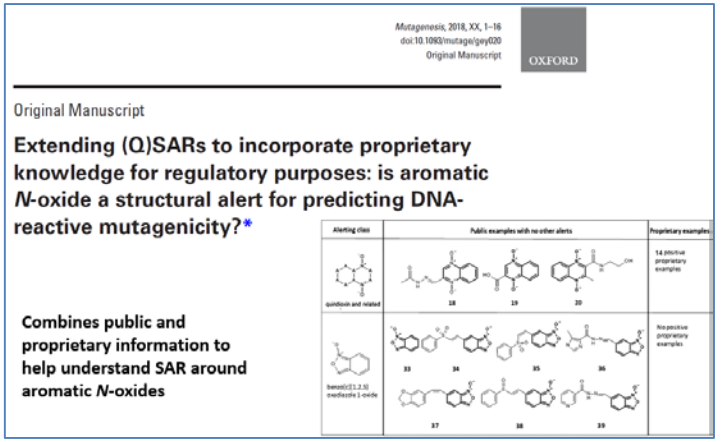
* Language added

Leadscope model applier Complete ICH M7 (Q)SAR Implementation

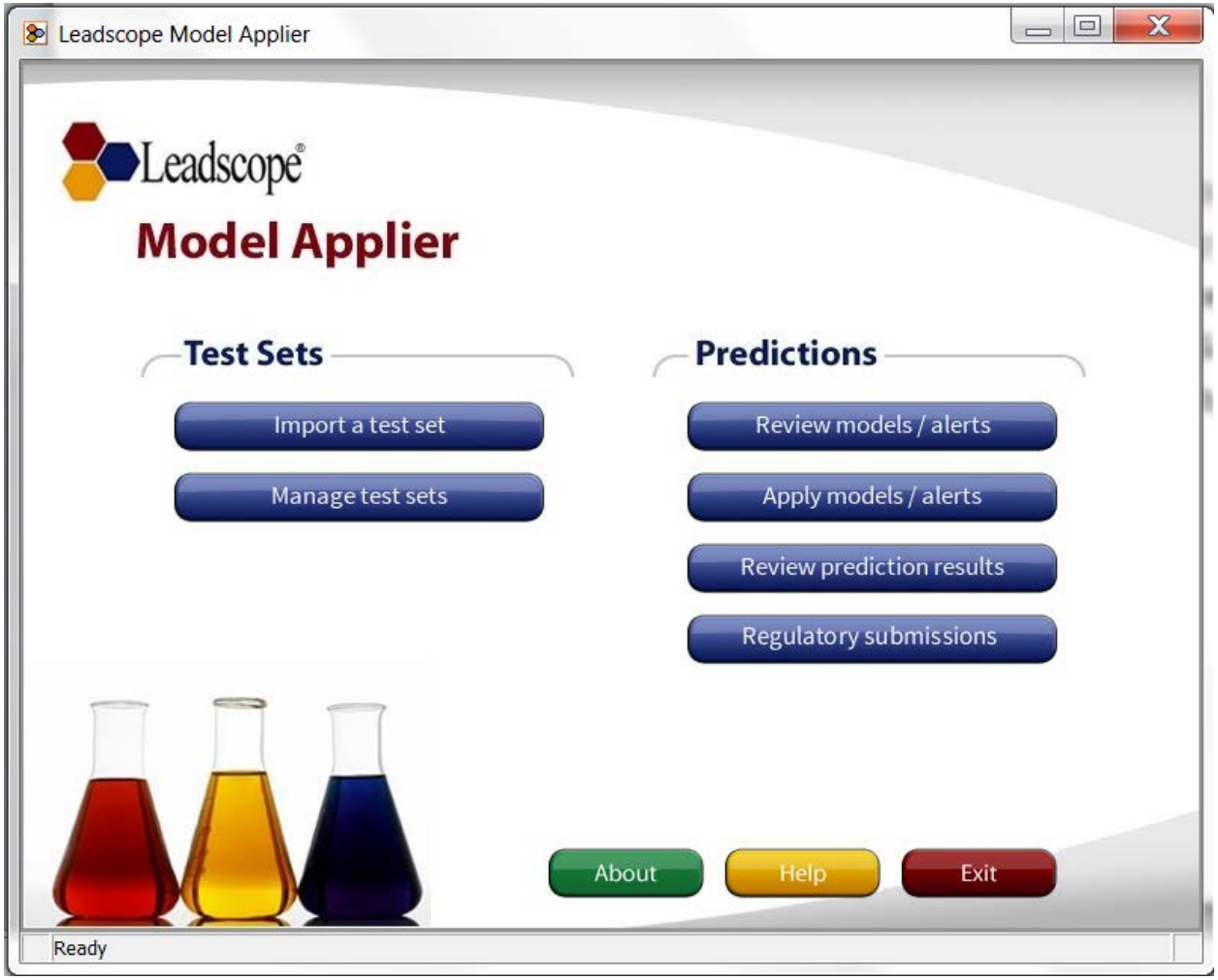
Capability	Leadscope products
Genetox database	• Leadscope® SAR genetox database
Carcinogenicity database	• Leadscope® SAR carcinogencity database
Expert rule-based model	• Leadscope® Genetox Expert Alerts
Statistical-based model	• Leadscope® Statistical QSAR Genetox suite
Expert review and documentation of results	• Regulatory submission tool

Supporting publications





Leadscope model applier demo



LEADSCOPE PRODUCTS AND TECHNOLOGY

Leadscope QSAR models

Genetic toxicity

- Genetox Suite*
  - Clastogenicity In Vitro
    - Chromosome Aberrations In Vitro
      - In Vitro Chrom Ab CHL
      - In Vitro Chrom Ab CHO
    - Sister Chromatid Exchange
      - SCE In Vitro
        - In Vitro SCE CHO
        - In Vitro SCE Comp
        - In Vitro SCE Other
  - Clastogenicity In Vivo
    - Chromosome Aberrations In Vivo
      - In Vivo Chrom Ab Comp
      - In Vivo Chrom Ab Other
      - In Vivo Chrom Ab Rat
    - Micronucleus In Vivo
      - In Vivo Micronuc Mouse
  - Gene Mutation
    - Mammalian In Vitro
      - HGPRT Mut
      - Mouse Lymphoma Act
      - Mouse Lymphoma Unact
    - Mammalian In Vivo
      - In Vivo Rodent DL Mut
      - In Vivo Rodent Mut
    - Microbial In Vitro
      - Bacterial Mut
      - E Coli - Sal 102 A-T Mut
      - Salmonella Mut

Carinogenicity

- Rodent Carcinogenicity Suite*
  - Carcinogenicity In Vitro
    - Cell Transformation
      - Cell Transform BALBc
      - Cell Transform C3H
      - Cell Transform Comp
      - Cell Transform SHE
  - Carcinogenicity In Vivo
    - carc female mouse
    - carc female rat
    - carc male mouse
    - carc male rat

Reproductive

- Reproductive Toxicity Suite*
  - Repro Rodent
    - Repro Female Mouse
    - Repro Female Rat
    - Repro Male Mouse
    - Repro Male Rat
    - Repro Mouse Sperm
    - Repro Rat Sperm

Neurotoxicity

- Neurotoxicity Suite*
  - Rodent Newborn Behavior
    - Pup Behavior Mouse
    - Pup Behavior Rat
    - Pup Behavior Rodent

Developmental

- Fetal Growth
  - Fetal Growth Retardation
    - Growth Retard Mouse
    - Growth Retard Rabbit
    - Growth Retard Rat
    - Growth Retard Rodent
  - Fetal Weight Decrease
    - Wt Dec Mouse
    - Wt Dec Rabbit
    - Wt Dec Rat
    - Wt Dec Rodent
- Fetal Survival
  - Fetal Death
    - Fetal Death Mouse
    - Fetal Death Rabbit
    - Fetal Death Rat
    - Fetal Death Rodent
  - Post-implantation Loss
    - Post Impl Loss Mouse
    - Post Impl Loss Rabbit
    - Post Impl Loss Rat
    - Post Impl Loss Rodent
  - Pre-implantation Loss
    - Pre Impl Loss Mouse
    - Pre Impl Loss Rabbit
    - Pre Impl Loss Rat
    - Pre Impl Loss Rodent
- Structural Dysmorphogensis
  - Dysmorph Mouse
  - Dysmorph Rabbit
  - Dysmorph Rat
  - Dysmorph Rodent
- Visceral Organ Toxicity
  - Visc Org Mouse
  - Visc Org Rat
  - Visc Org Rodent

Cardiological

- Human Adverse Cardiological Effects Suite*
  - Cardiological Effects
    - Arrhythmia
    - Bradycardia
    - Conduction Disorder
    - Coronary Artery Disorder
    - Electrocardio Abnorm
    - Heart Failure
    - Myocardial Disorder
    - Myocardial Infarct
    - Palpitations
    - QT Prolongation
    - Rate Rhythm Abnorm
    - Tachycardia
    - Torsades

Hepatobiliary

- Human Adverse Hepatobiliary Effects Suite*
  - Hepatobiliary Effects
    - Bile Duct Disorder
    - Cholestasis
    - Liver Damage
    - Liver Enzyme Abnorm

Urinary tract

- Human Adverse Urinary Effects Suite*
  - Urinary Tract Effects
    - Bladder Disorder
    - Blood in Urine
    - Kidney Funct Test Abnorm
    - Nephropathy
    - Renal Disorder
    - Urolithiasis

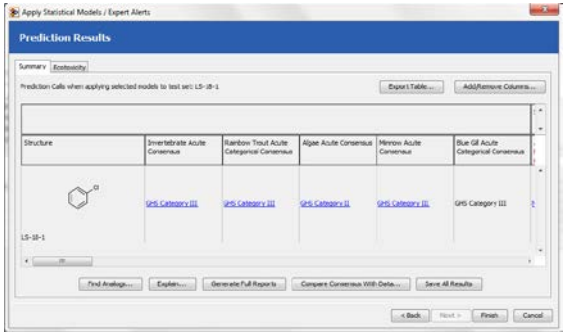
* developed under collaboration with U.S. FDA

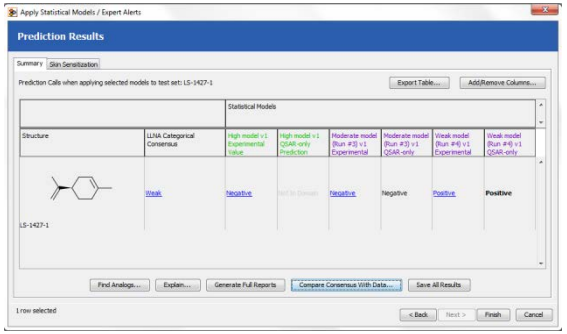
New statistical and expert alert models

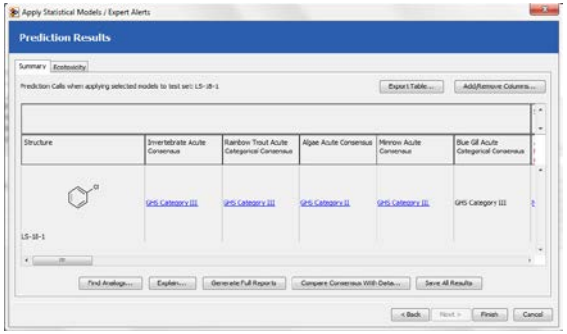
- **Acute toxicity**
  - Predicts Globally Harmonized System (GHS) categories
  - Uses statistical models and expert alerts

- **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





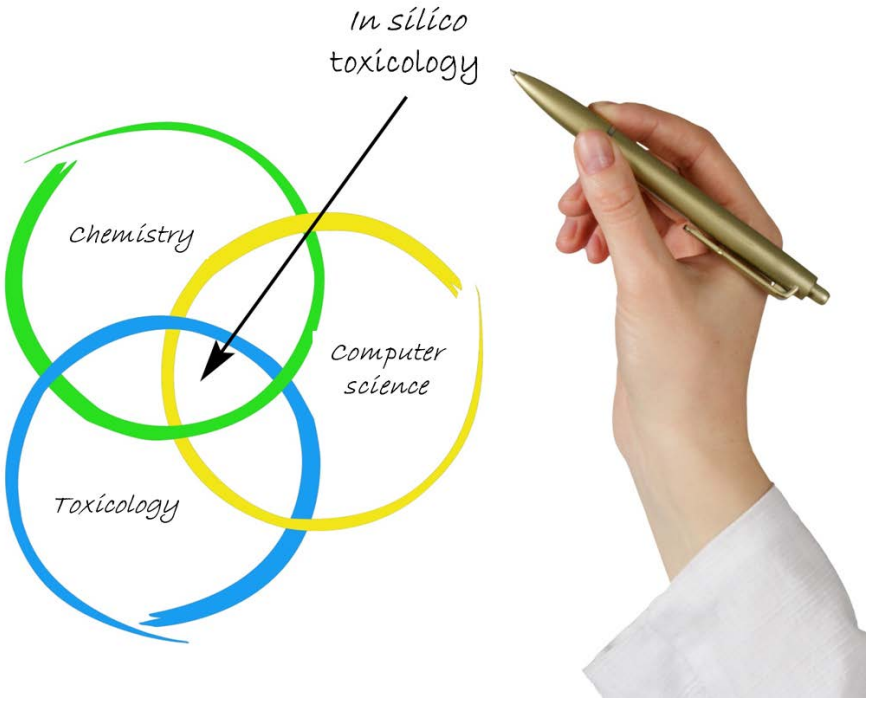


Leadscope Databases

Leadscope Toxicity Database	Over 190,000 chemical records with over 400,000 toxicity studies from literature sources, including - acute and repeated dose toxicity studies - reproductive and developmental toxicity studies - skin & eye sensitivity and irritation
SAR Carcinogenicity Database	High quality carcinogenicity database, includes 3,596 compounds with 11,538 test results
SAR Genetox Database	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!