FDA Predictive Toxicology Roadmap
Comments

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Kevin P. Cross, Ph.D. (kcross@leadscope.com)
Leadscope, Inc.
Who is Leadscope?

• Long-time FDA research collaborator (CRADA, RCAs CDER, CFSAN)
• Computational toxicology database builder and provider
• Computational toxicology software vendor
  • (alerts, statistical (Q)SAR, read-across, expert review, decision support, reporting)
• An industry leader in promoting acceptance of *in silico* methods through collaborative development of standards (incorporating multiple predictions, experimental data, and expert analysis).
• Proponent of 3Rs (replacement, reduction, refinement) of animal testing
How to identify promising new technologies in predictive toxicology?

- Papers, conferences, communication - finding interesting research
- Waiting for sponsor proposals – a sponsor-motivated approach
- Short-term project collaborations – addressing a specific problem
- Big picture collaborations – what are the problems to be solved?
Big Picture Collaborations for Computational Toxicology
Applications that currently can benefit from *in silico* methods

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As a regulatory submission – example regulations

• Alternative methods for filling data gaps are outlined European Union’s REACH regulation [1]
• Residues of pesticides or their metabolites [2]
• The ICH M7 guideline for drug impurities [3]
• United States, Frank R. Lautenberg Chemical Safety for the 21st Century Act revision to the Toxic Substance Control Act (TSCA) [4]
• The United States Food and Drug Administration (US FDA) Center for Device and Radiological Health (CDRH) guidance for industry and FDA staff on for the use of International Standard ISO 10993-1 for biological evaluation of medical devices[5]
• The FDA draft guidance on Electronic Nicotine Delivery Devices (ENDS) discusses the use of computational toxicology models [6]

ICH M7 Impurity Guideline

As of May 2017, 31 New Molecular Entities approved with (Q)SAR* and 488 impurities evaluated*

* Powley, M.W., (Q)SAR Evaluation of Potentially Mutagenic Impurities: Regulatory Experience with Out of Domain Results, Presented at the GTA Conference May 2017
Principles and procedures for implementation of ICH M7 recommended (Q)SAR analyses

21 Organizations collaborated, including regulatory agencies, pharmaceutical companies, (Q)SAR developers and consultants

Outlines a protocol for mutagenicity (Q)SAR implementation aligned with the ICH M7 guideline
Principles and procedures for implementation of ICH M7 recommended (Q)SAR analyses

- How to identify data
- What data to look for
- Where to look for data
- How to assess study quality
- How to document study results
Principles and procedures for implementation of ICH M7 recommended (Q)SAR analyses

15 case studies

Describes how to document the (Q)SAR results and expert review
In silico toxicology (IST) protocol consortium

- An international consortium of over 50 members including regulators, government agencies, industry, academics, model developers, and consultants across many different sectors
- This consortium initially developed the overall strategy
- Working subgroups are developing individual in silico toxicology protocols for major toxicological endpoints, including genetic toxicity, carcinogenicity, acute toxicity, reproductive toxicity, developmental toxicity, ...
Supported by:
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In silico toxicology protocols:

**In silico toxicology project**

- The standardization of *in silico* tool use and interpretation
- Reduce the burden on both industry and regulators to provide justification for the use of these methods
- Results can be generated, recorded, communicated, and archived in a uniform, consistent, and reproducible manner
- Incorporating these principles routinely into the use of *in silico* methods will support a more transparent analysis of the results and mitigate “black box” concerns
- Provides an important step towards a quality-driven science for *in silico* toxicology
General Strategy

**In silico toxicology protocol**

1. **Toxicological effects/mechanisms assessment**
   - a. Select *in silico* methods and data sources
   - b. Collect experimental data and generate predictions
   - c. Generate the overall assessments*
   - d. Assign the reliability scores*

2. **Toxicological endpoints assessment**
   - a) Generate the endpoint assessments*
   - b) Determine confidence scores*
   - c) Document the results

* Based on rules/principles outlined in the in silico toxicology protocols, including an expert review if warranted

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AOPs  IATAs  Defined approaches  Tiered approaches
Protocols in development for 20 major toxicological endpoints

- Skin/respiratory sensitization
- Carcinogenicity
- Reproductive/developmental toxicity
- Acute toxicity/lethality
- Endocrine activity
- Liver toxicity
- Cardiac toxicity
- Neurotoxicity
- Repeated dose
- Bone marrow toxicity
- Renal toxicity
- Gastrointestinal toxicity
- Respiratory system toxicity
- Skin/eye irritation/corrosion
- Physical hazards
- Ecotoxicity
- Photosensitization/phototoxicity
- Immunotoxicity
Conclusion

• *In silico* toxicology is a fast and inexpensive approach to support toxicological assessments as well as reducing animal testing

• It is already accepted as part of regulatory submissions

• Protocols provide support for implementation of *in silico* toxicology
  • Standardization of *in silico* tool use and interpretation
  • Reduce the burden on both industry and regulators to provide justification for the use of these methods
  • Results generated, recorded, communicated, and archived in a uniform, consistent, and reproducible manner for regulatory use

• Please join us in a collaborative approach to solving big *In silico* issues!