FDA Predictive Toxicology Roadmap Comments

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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

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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?

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Big Picture Collaborations for Computational Toxicology

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Applications that currently can benefit from *in silico* methods

- ***As a regulatory submission***
- ***As part of the weight of evidence in regulatory studies***
- ***Mixtures assessment***
- ***Assessment of impurities and degradation products***
- ***Residues of pesticides***
- ***Assessment of extractables and leachables***
- ***Workers' safety and occupational health***
- ***Metabolite analysis***
- ***Ecotoxicity***
- ***Classification and labeling***
- ***Green chemistry and safer alternatives***
- ***Selection of product development candidates***
- ***Emergency response situations***
- ***Prioritizing testing of chemicals***
- ***Rationalization of in vivo or in vitro study results***

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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]

[1] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02006R1907-20161011&from=EN
[2] http://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX%3A32009R1107
[3] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_Step_4.pdf
[4] https://www.congress.gov/bill/114th-congress/senate-bill/697/all-info
[5] https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf
[6] https://www.fda.gov/downloads/tobaccoproducts/labeling/rulesregulationsguidance/ucm499352.pdf

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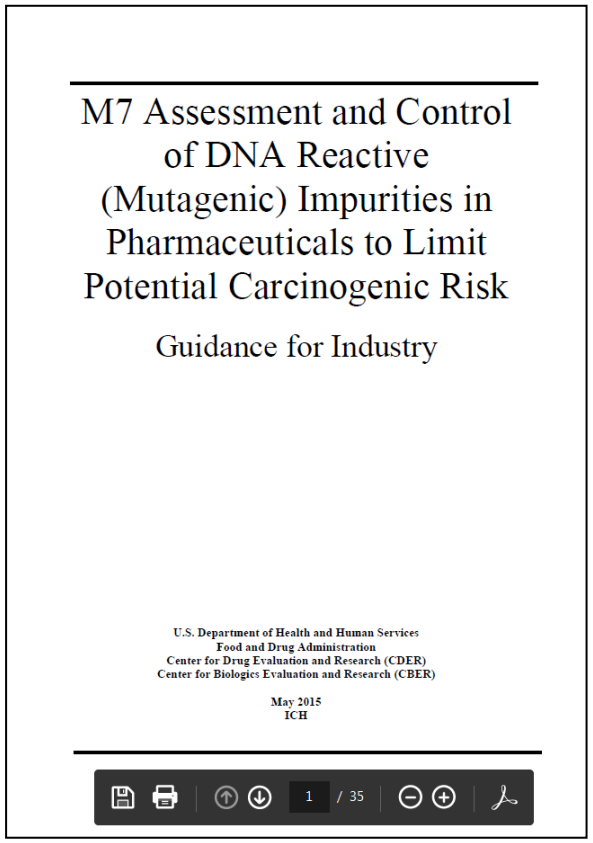
ICH M7 Impurity Guideline


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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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

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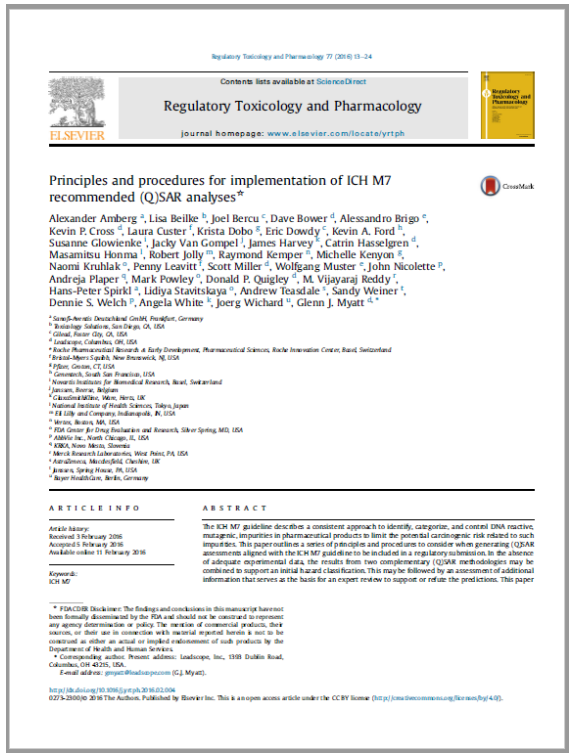
Principles and procedures for implementation of ICH M7 recommended (Q)SAR analyses



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Principles and procedures for implementation of ICH M7 recommended (Q)SAR analyses*

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ABSTRACT

The ICH M7 guideline describes a consistent approach to identify, categorize, and control DNA reactive, mutagenic, impurities in pharmaceutical products to limit the potential carcinogenic risk related to such impurities. This paper outlines a series of principles and procedures to consider when generating (Q)SAR assessments aligned with the ICH M7 guideline to be included in a regulatory submission. In the absence of adequate experimental data, the results from two complementary (Q)SAR methodologies may be combined to support an initial hazard classification. This may be followed by an assessment of additional information that serves as the basis for an expert review to support or refute the predictions. This paper

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0273-2300/© 2016 The Author. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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

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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

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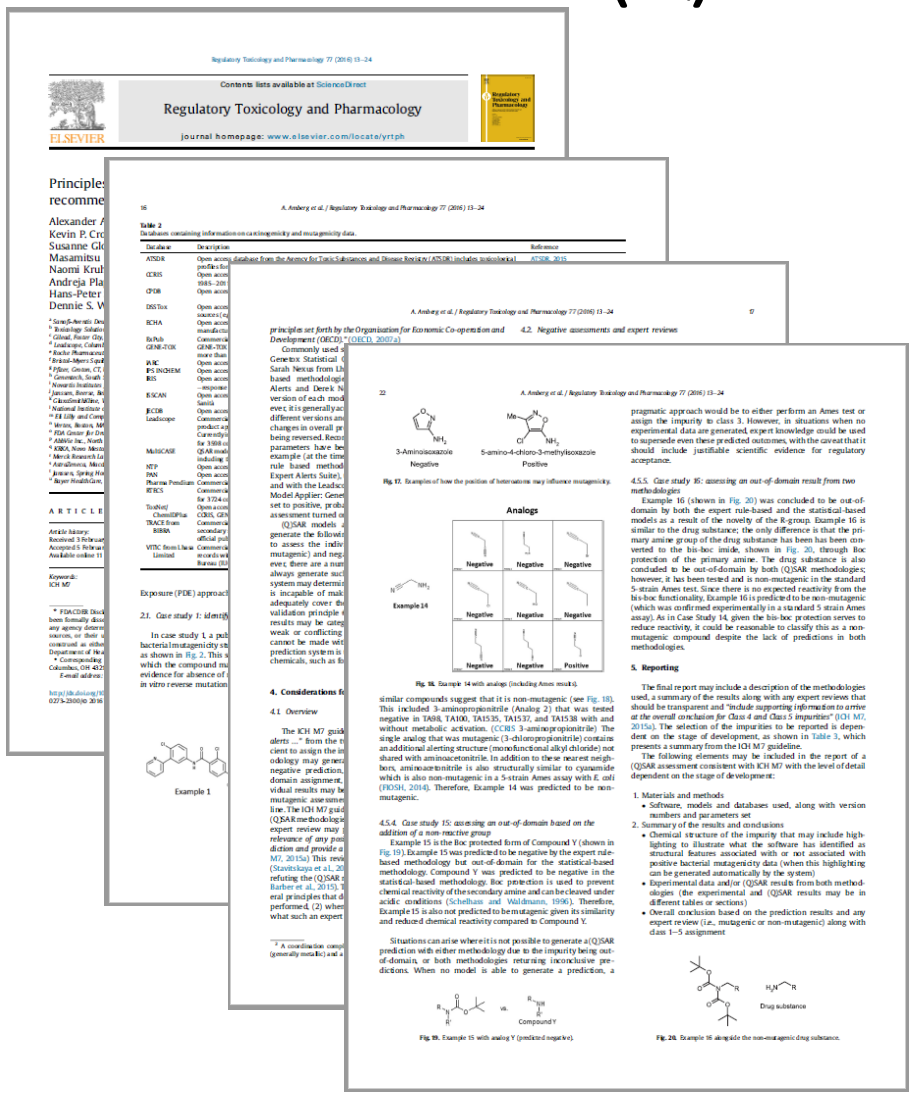
Principles and procedures for implementation of ICH M7 recommended (Q)SAR analyses



15 case studies

Describes how to document the (Q)SAR results and expert review

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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, …

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In silico toxicology protocols

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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

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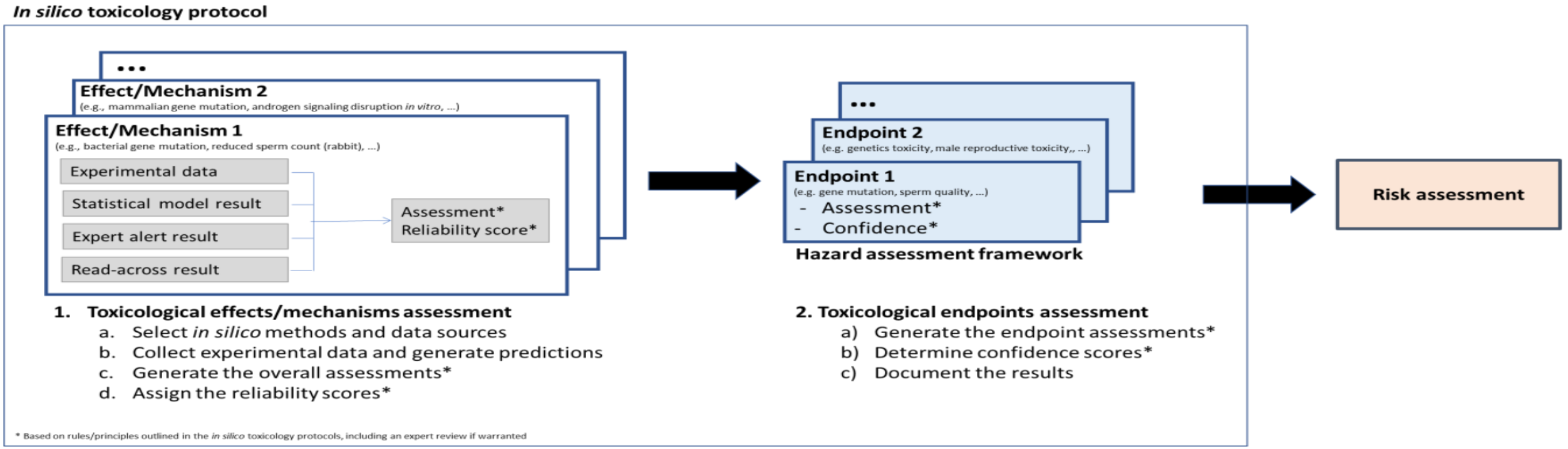
General Strategy



AOPs IATAs Defined approaches Tiered approaches

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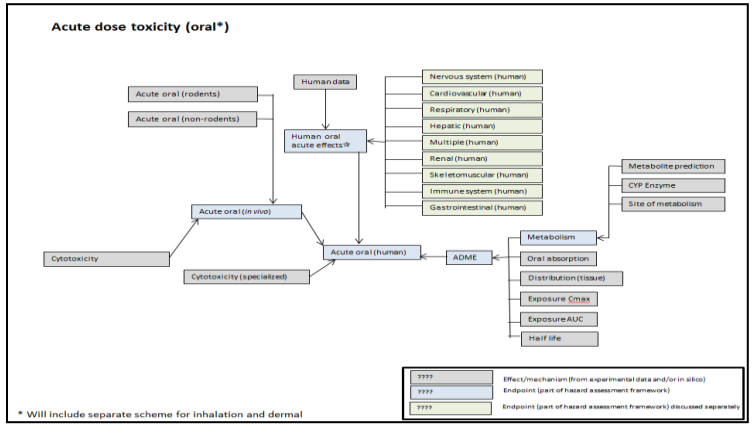
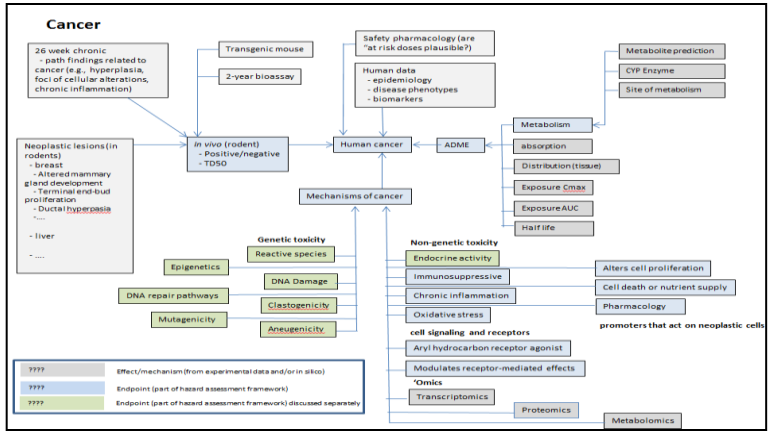
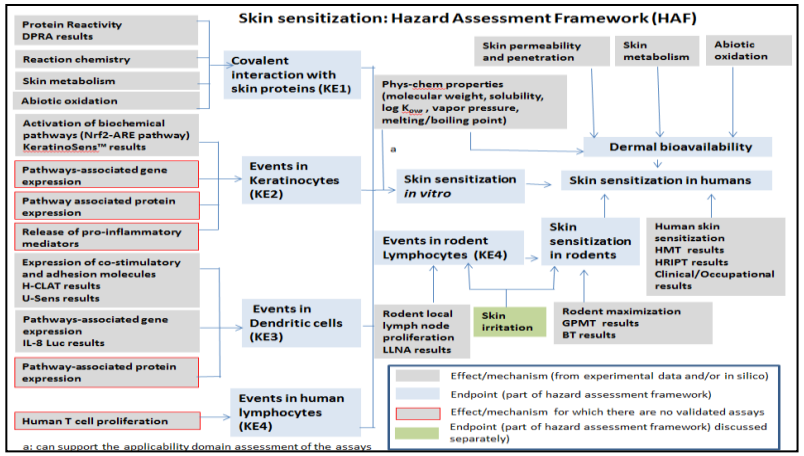
Protocols in development for 20 major toxicological endpoints

- 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







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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!**

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