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Computational tools to predict the pesticide toxicity

- **Bharath BR** **Ph.D**

Background

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United States Environmental Protection Agency

- In 2020, US EPA - Toxic Substances Control Act (TSCA) was charged to evaluate the toxicity of over 85,000 chemicals that are produced, imported, or managed in the U.S. (TSCA, 2020).

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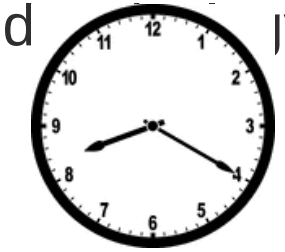


*Not effective in keeping up with the constantly growing chemical inventory.

- The US EPA cheminformatics-based, open access computational toxicology tools were developed to supplement, support or even replace *in vivo* bioassays.

Background

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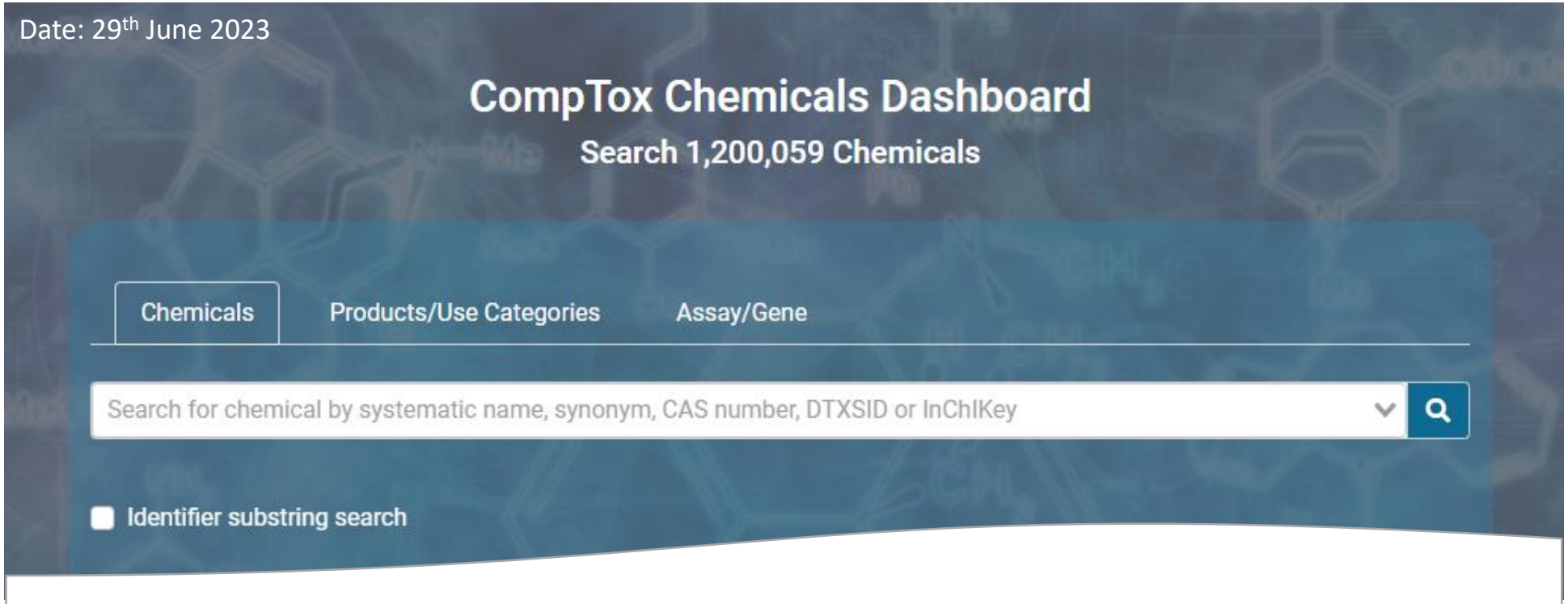

- Provides data that have been modeled for chemical screening and prioritization, hazard identification, determination of mode of action (MOA) and risk assessment.

https://comptox.epa.gov/dashboard/

Reasons for Regulatory Needs : Consumer Perspective

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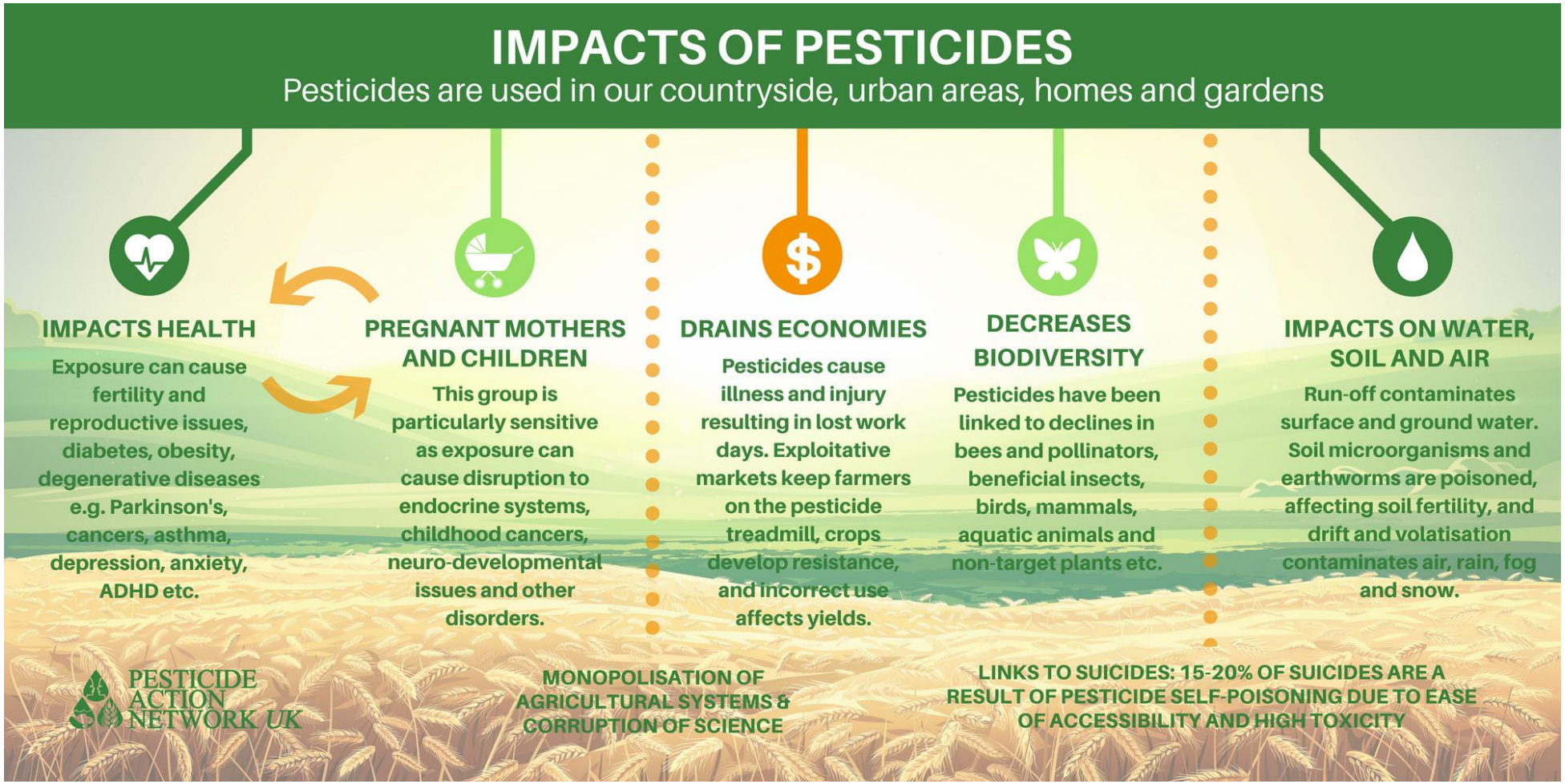

Source: https://www.challenge.org/resources/pesticide-use-in-farming/

Pesticides and Regulatory Challenges : Registrant's Perspective

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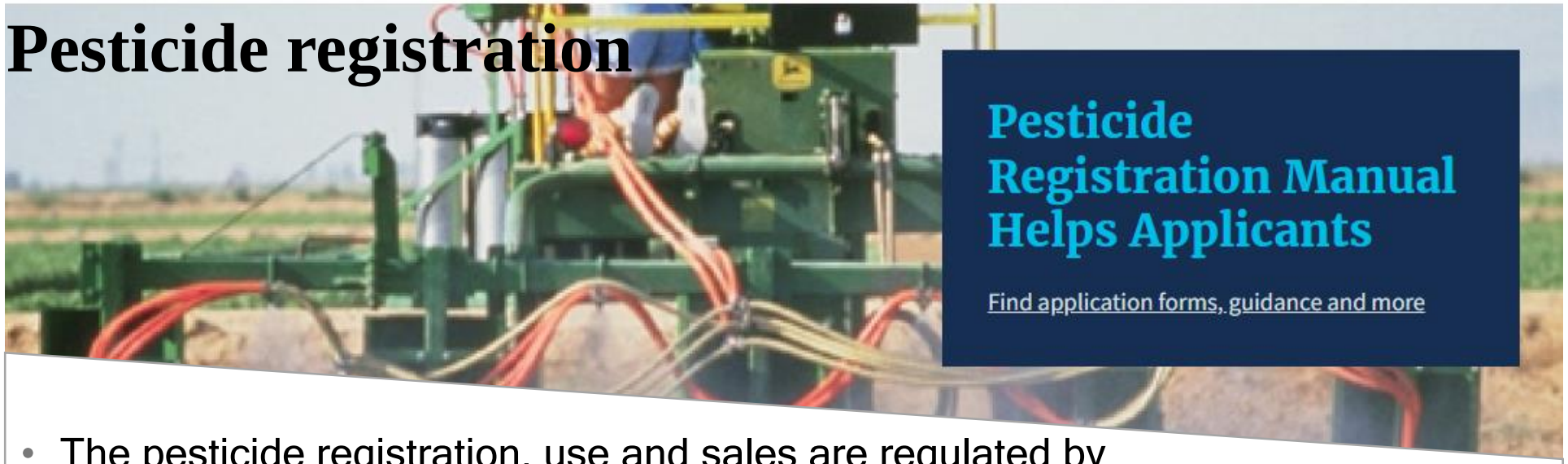
Pesticide registration



- The pesticide registration, use and sales are regulated by
  - The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA),
  - The Federal Food, Drug and Cosmetic Act,
  - The Food Quality Protection Act,
  - The Pesticide Registration Improvement Act and
  - The Code of Federal Regulations Title 40 (40CFR).

- Specific laws and regulations regarding pesticide registration, use and sales also apply within individual states.

Pesticides and Regulatory Challenges : Registrant's Perspective

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Central Insecticides Board & Registration Committee (CIB&RC)

Pesticides and Regulatory Challenges

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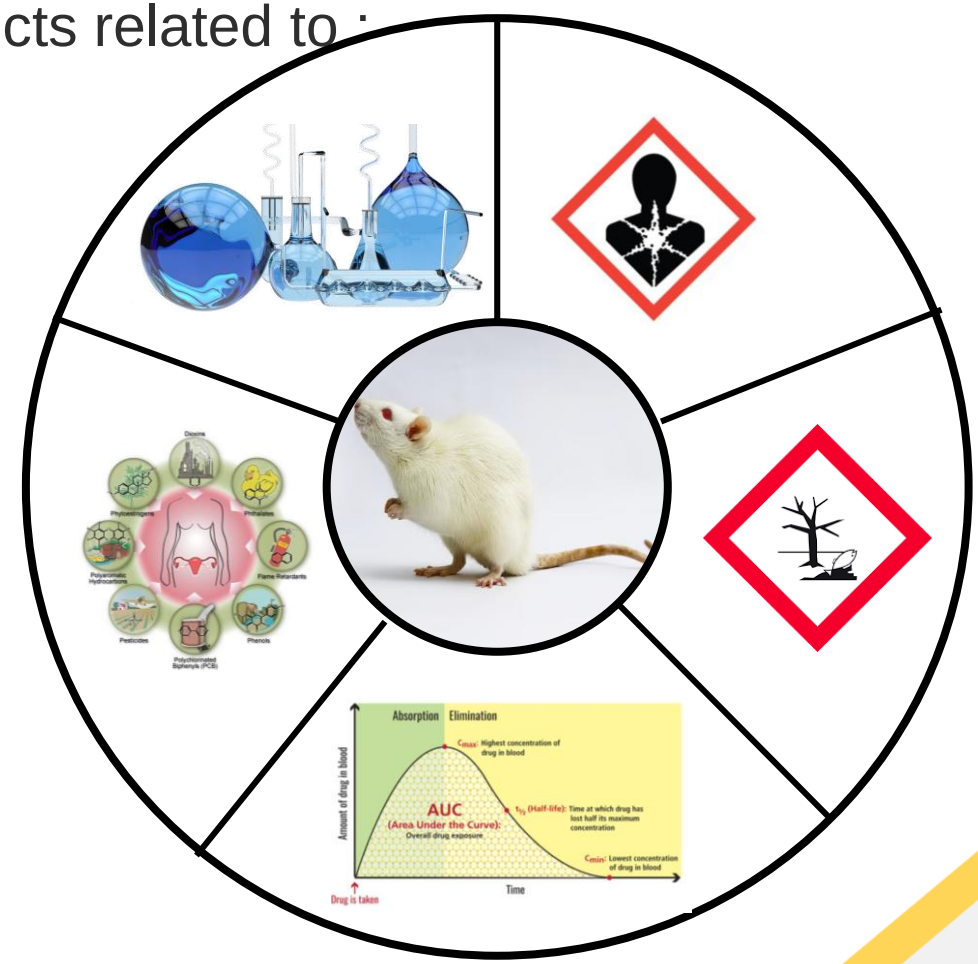
As part of this process, pesticide registrants submit Health Effects Test Guidelines studies (US EPA, 1998), to evaluate effects related to :

- Skin Sensitization
- Eye irritation
- Carcinogenicity,
- Genotoxicity,
- Development,
- Reproduction,
- Endocrine systems,
- Neurotoxicity,
- Immunology and other outcomes.

*Screening program



Predictive Chemistry Using Computational Tools

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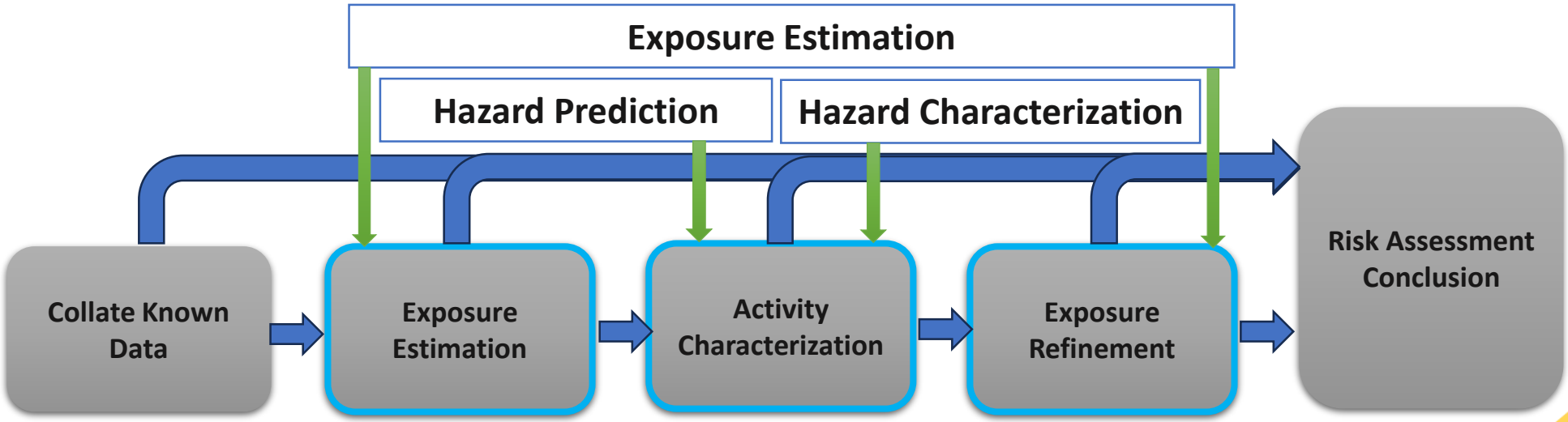
- Computational tools **can be used** when the ability to generate new data is limited, by cost, time or regulatory framework.
- In silico predictions can
  - **Support** risk assessment
  - **Add** weight of evidence
  - **Reduce** uncertainty
- In silico methods should be well documented to maintain transparency.
- Applicability domain should be well understood based on the data on which model is built.



Computational Approaches

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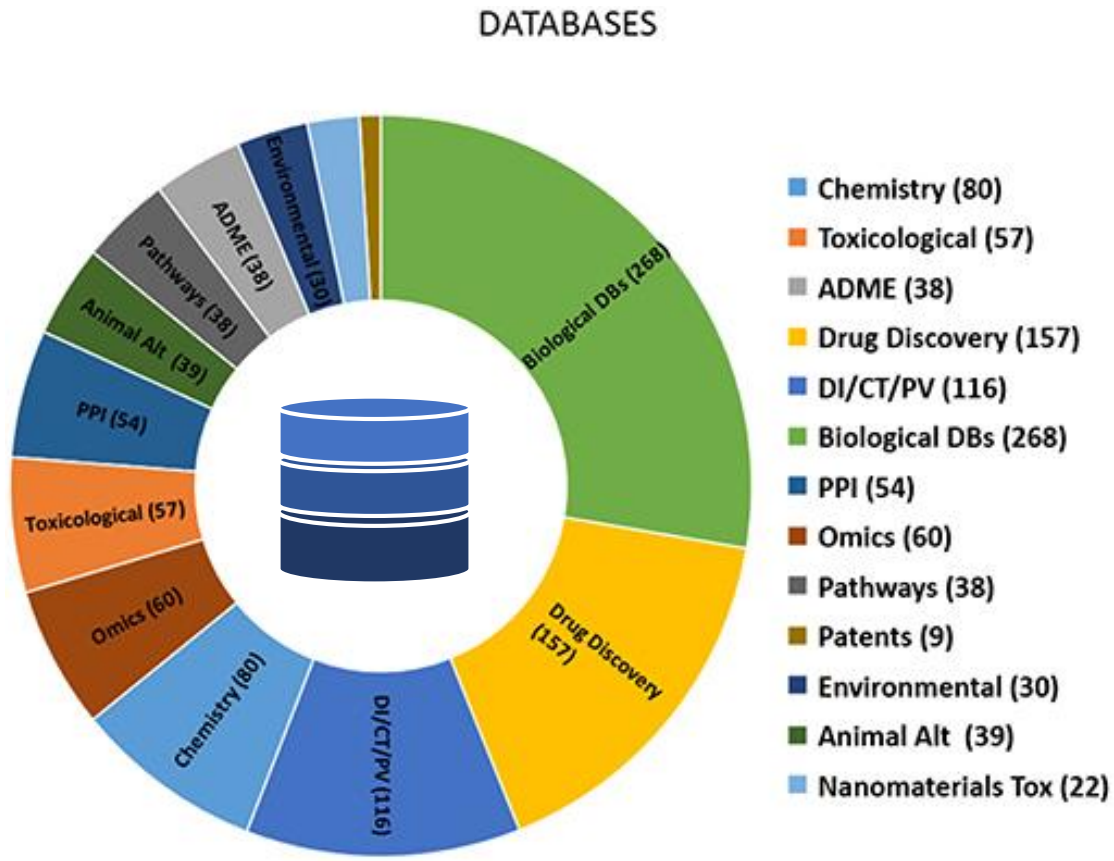
Quantitative Structure-Activity Relationship ([Q]SAR)
Qualitative Structure-Activity Relationship ([Q]SAR)

The best way to predict the future is to study the past, or prognosticate

Robert Kiyosaki

Learn from the past prepare for the future

Thomas S. Monson



QSAR: Quantitative Structure Activity Relationship

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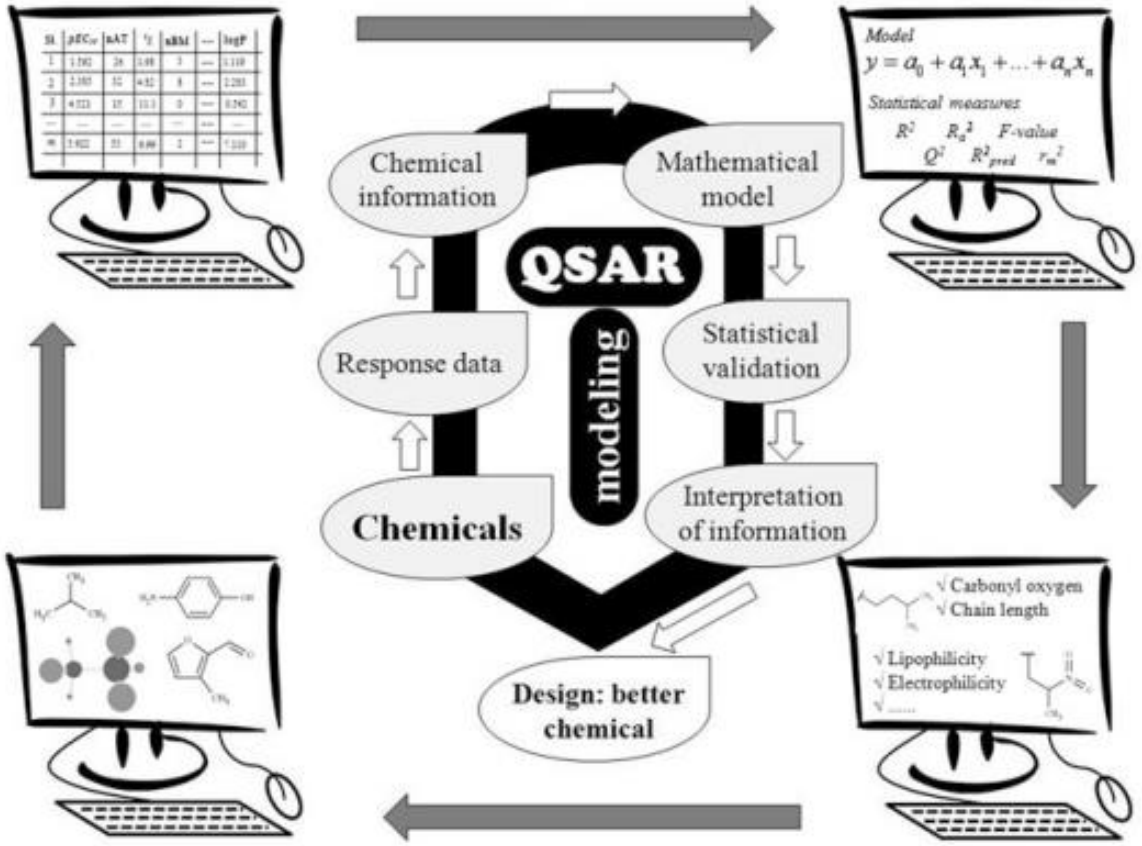
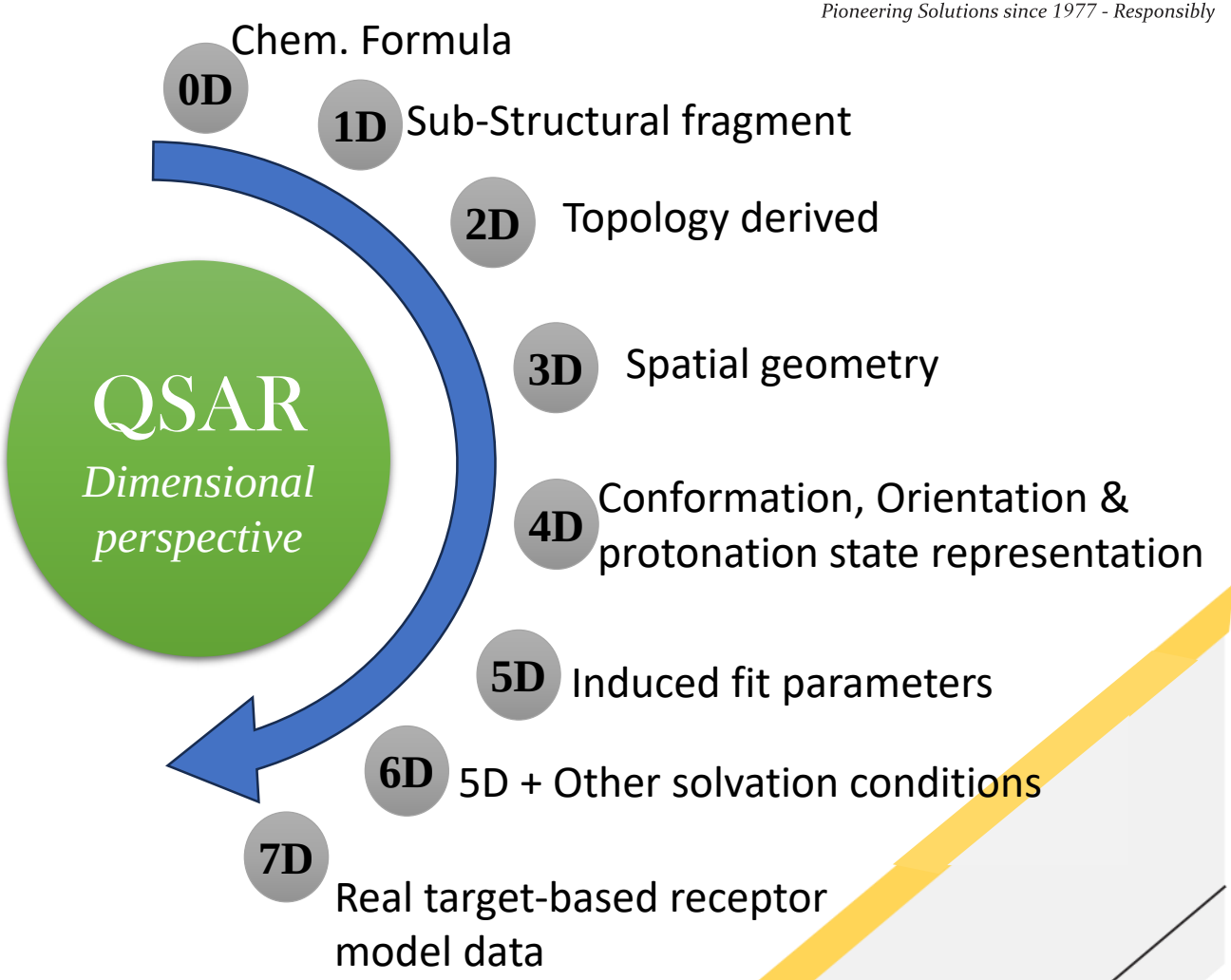


Kunal et al., 2015



A Simple Analogy to Understand Dimensions of QSAR

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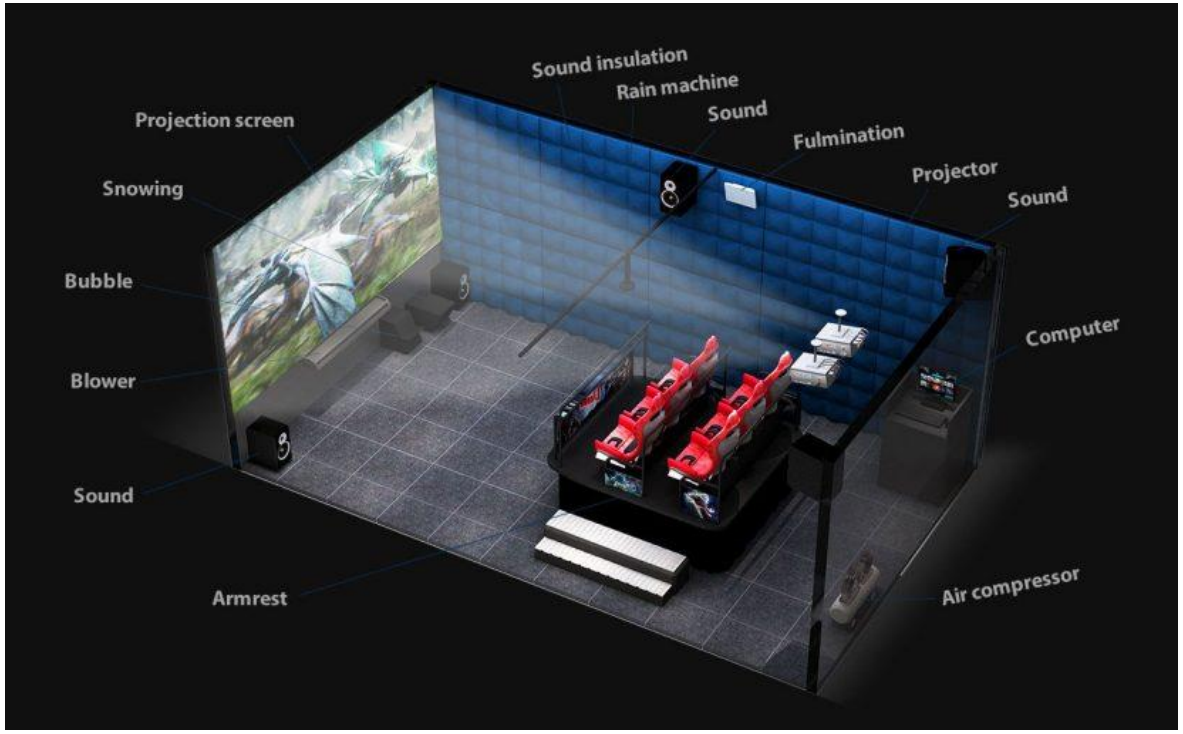
The regular screen



The virtual reality

QSAR Descriptors

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The descriptors are correlated with the activities to obtain a statistically significant QSAR model.

Dimension of descriptors	Parameters
0D-descriptors	Constitutional indices, molecular property, atom and bond count
1D-descriptors	Fragment counts, fingerprints
2D-descriptors	Topological parameters, structural parameters, physicochemical parameters including thermodynamic descriptors
3D-descriptors	Electronic parameters, spatial parameters, molecular shape analysis parameters, molecular field analysis parameters and receptor surface analysis parameters

Typical Process of QSAR Modelling

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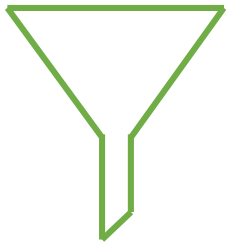
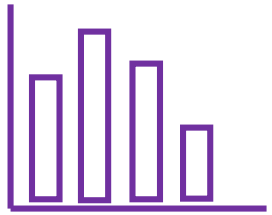
Source Data



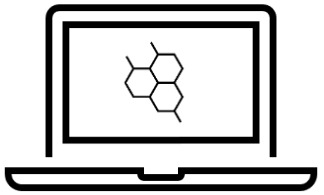
Curate Data

Partition Data into Training & Test

Develop Model



Validate Model (Internal & External)



Run New Data

Use Prediction

Develop

Apply

Reference: AFSA

Read-across approach

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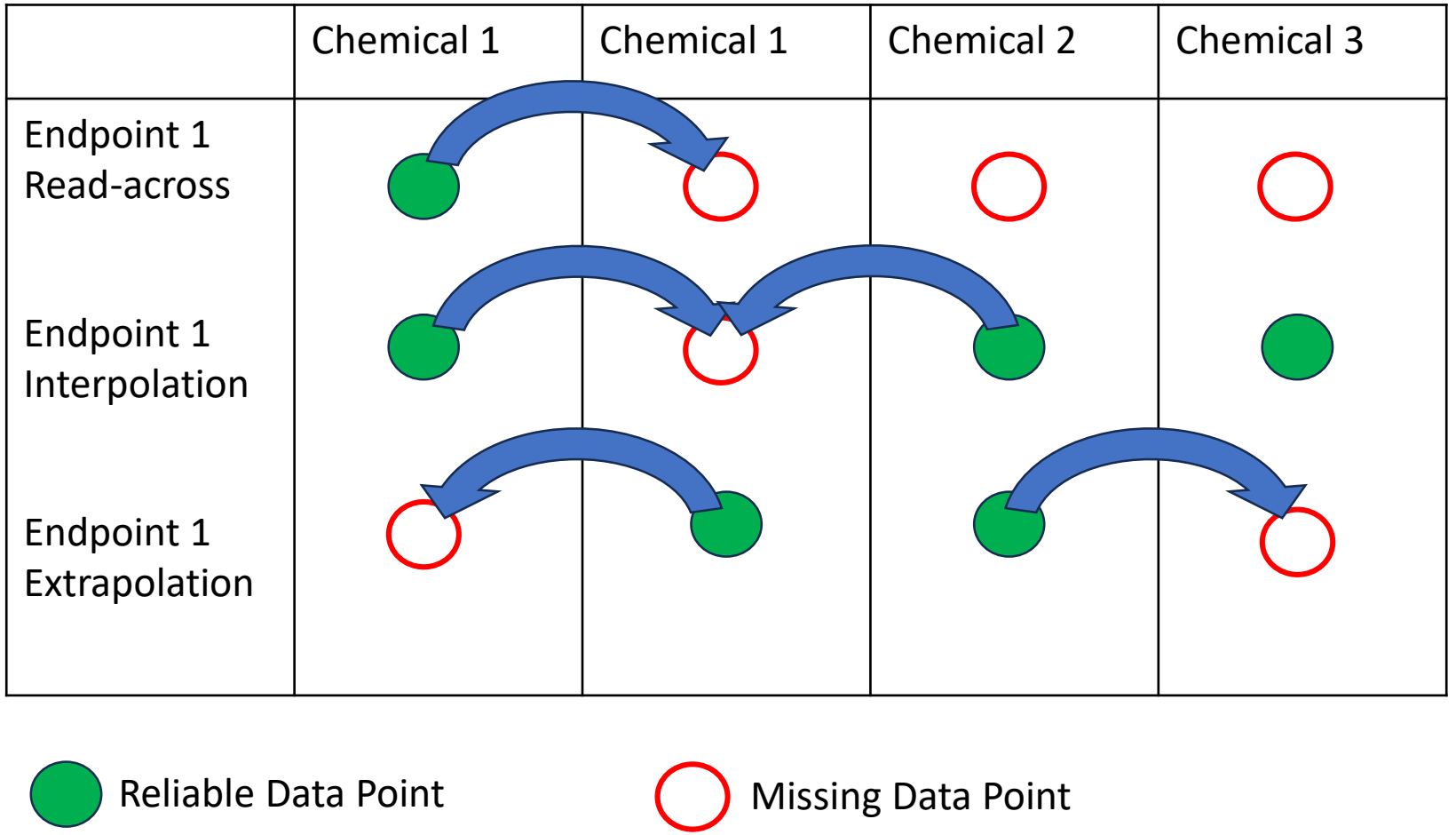

- An alternative approach to fill a data gap for a substance (Target), for a specific endpoint, by using the data from another structurally/ mechanistically similar substance (Source)

Read-across approach

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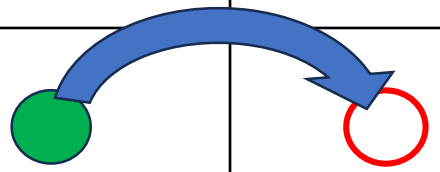
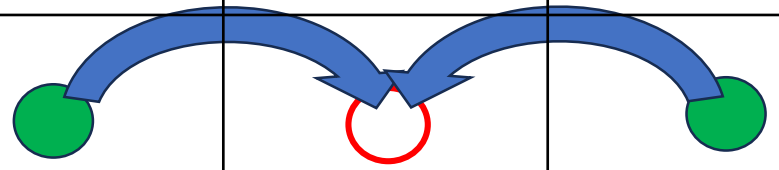
One- to- One read across

	Substance 1	Substance 2
Endpoint 1 Read-across		

Many- to- One read across

	Substance 1	Substance 2	Substance 3
Property			

Multiple source substances, No similar trend or pattern in their properties = **Analogue** approach

Multiple source substances, similar trend or pattern in their properties = **Group** (Category)

	C8	C10	C8-C14	C12	C12-C14	C12-C18	C18
Property							

The Read-across process / Framework

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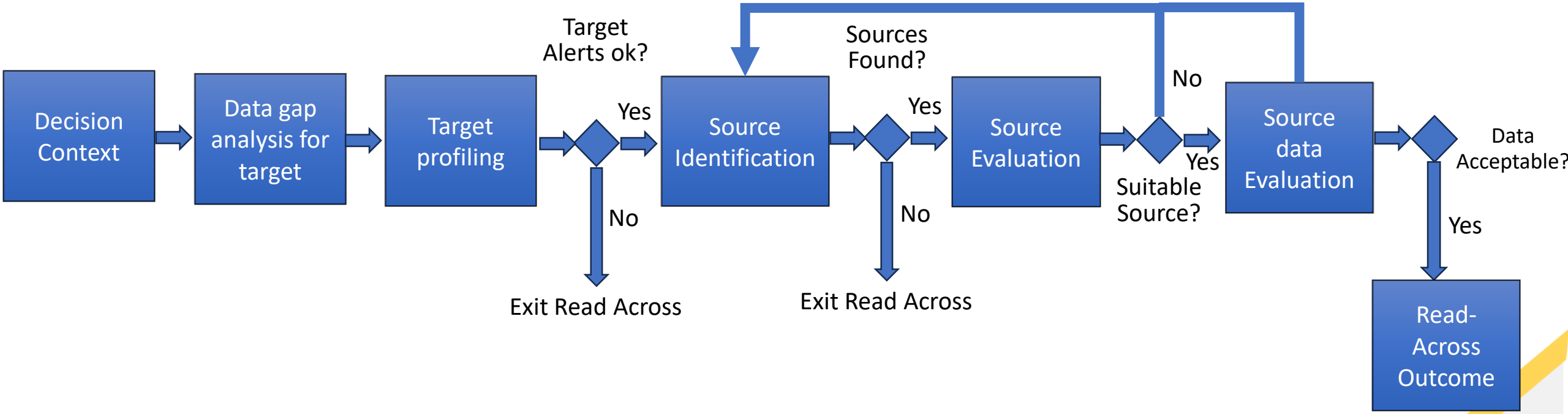

QSAR Based Predictive Toxicology Tools Available

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QSAR TOOLBOX

Derek nexus

MultiCASE

VEGAHUB

Sarah nexus

OPERA

OPEn (q)saR App

Leadscope®

Toxtree

Danish (Q)SAR Database

Choosing the Model

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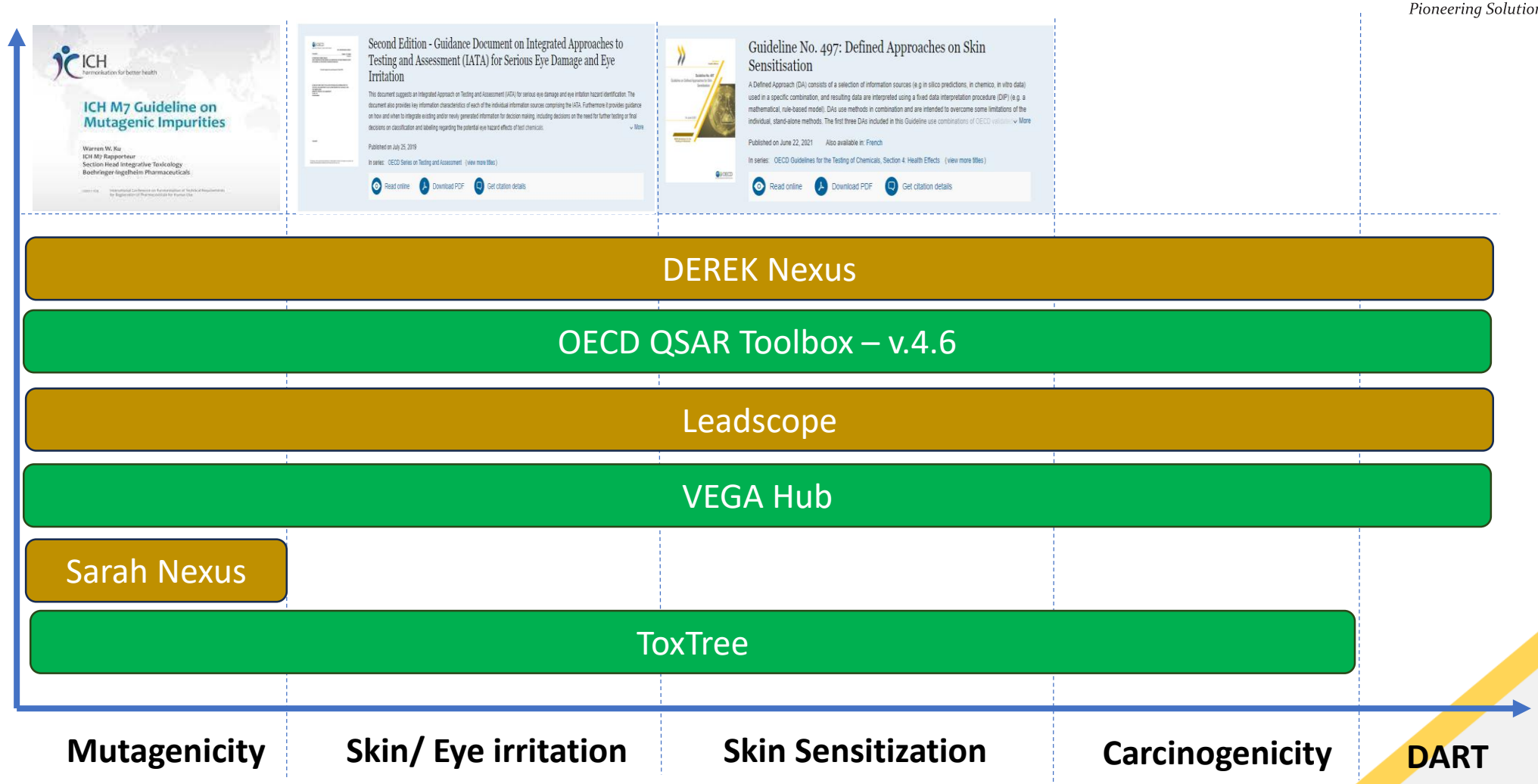

License Required

Freely available

Assessing reliability

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Applicability Domain	Uncertainty	Variability	Validation	Reporting
Depends on the training set used to develop the model	Expresses the limitation in knowledge or lack of data. Can be reduced or eliminated	Refers to inherent heterogenicity in the data. Cannot be reduced but can be characterized.	Allows to evaluate the predictivity and reliability of the model. Can be internal or external	QSAR Model Reporting Format (QMRF) is a harmonized template structured according to the OECD validation principles

Be transparent about what the prediction can tell / cannot tell

Limitations of computational predictions

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- Dependency on data availability
- Analyzing/ prediction of toxicity for multi-constituents/ formulations.
- Prediction for UVCB

Summary

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- In-silico models can be used to predict toxicity.
- The right approach/model need to be used for the reliable prediction.
- During the prediction make sure that, you know the identity of the target chemical.
- Choose a model that is appropriate for both target chemical type and endpoint of interest.
- Check the target chemical is with in applicability domain.
- With all these considerations, use computational models to reduce the time, cost and animals.

- Wish you all a Happy prediction!!!!!!

Services offered by JRF

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Predictive Toxicity

- Physicochemical properties
- Environmental Fate and Transport
- Ecotoxicity endpoints
- Human Health Hazard endpoints
- Endocrine Disruption Potential
- ADME

Ligand based drug discovery

- Customized 2D and 3D QSAR Modelling for the prediction of toxicity and efficacy
- Pharmacophore modelling for the prediction of toxicity and efficacy
- Library enumeration for lead optimization

Structure based drug discovery

- Molecular docking to understand the protein ligand (Small molecule drug/chemical) interaction.
- MD simulation to understand the protein quality, stability of drug and protein interaction in solvated system.
- Receptor based pharmacophore modeling

Prediction of MoA for Pesticides

- Screening of insecticides for MoA against JRF's insecticides library
- Screening of fungicides for MoA against JRF's fungicides library
- Screening of herbicides for MoA against JRF's herbicides library

Protein modeling and simulation

- Modelling of protein structure and validation
- Active pocket/binding site prediction
- Residue substitution analysis to understand the impact of mutation on target protein structure/function.

In Vitro

- Skin Corrosion Test
- Skin Irritation Test
- Eye Irritation test
- 3T3 NRU Phototoxicity Test
- Skin Sensitization Tests
- Photosensitization
- ADME

Ex-vivo

- Bovine Corneal Opacity and Permeability Test
- Dermal Absorption

Thank you!

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Supplementary Slides for the Audience Reference

Software for the prediction toxicological endpoints

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SOFTWARE (AND DEVELOPER)	AVAILABILITY	ENDPOINT										
		Acute oral toxicity	Repeat dose (chronic) oral toxicity	Genotoxicity (including mutagenicity)	Carcinogenicity	Reproductive (including developmental) toxicity	Endocrine activity / disruption	Hepatotoxicity	Nephrotoxicity (+ urinary tract toxicity)	Neurotoxicity	Cytotoxicity	Immunotoxicity (3)
ACD/Tox Suite (ToxBoxes)	Commercial	•		•			•					
ADMET Predictor (Simulations Plus Inc.)	Commercial		• (1)	•	•		•	•				
BioEpisteme	Commercial				•			•	•			
Caesar project models (Mario Negri Institute)	Freely available			•	•	•						
Derek (Lhasa Ltd)	Commercial			•	•	•	•	•	•	•		•
HazardExpert (CompuDrug)	Commercial			•	•					•		•
Lazar (In Silico Toxicology; Freiburg university)	Freely available		• (1)	•	•			•				
Leadscope (Leadscope)	Commercial			•	•	•		•	•	•		
MCASE/MC4PC (MultiCASE)	Commercial	•	•		•	•	•	•	•		•	
MDL QSAR (MDL)	Commercial	•	• (1)	•	•			•	•			
OASIS-TIMES (Laboratory of Mathematical Chemistry, Bourgas University)	Commercial			•			•					
OncoLogic (US EPA)	Freely available				•							
Pallas Suite including ToxAlert, Cytotoxicity (CompuDrug)	Commercial			•	•					•	•	
TerraQSAR (TerraBase)	Commercial	•					•					
TOPKAT (Accelrys)	Commercial	•	•	•	•	•						
Toxtree (JRC)	Freely available		• (2)	•	•							
Molcode Toolbox (Molcode Ltd)	Commercial		•	•	•		•				•	

(1) Maximum tolerated dose in humans;
(2) Cramer classification tree;
(3) Immunotoxicity other than skin sensitization;
(4) Prediction of the mutagenic index for Ames test mutagenicity

Software for the prediction toxicological endpoints

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SOFTWARE (AND DEVELOPER)	AVAILABILITY	ENDPOINT						
		Skin sensitization	Skin irritation	Skin corrosion	Eye irritation	Respiratory sensitization	Eye corrosion	Phototoxicity
ACD/Tox Suite (ToxBoxes)	Commercial		•		•			
ADMET Predictor (Simulations Plus Inc.)	Commercial							
BioEpisteme	Commercial							
Caesar project models (Mario Negri Institute)	Freely available	•						
Derek (Lhasa Ltd)	Commercial	•	•		•	•		•
HazardExpert (CompuDrug)	Commercial		•		•			
Lazar (In Silico Toxicology; Freiburg university)	Freely available							
Leadscope (Leadscope)	Commercial							
MCASE/MC4PC (MultiCASE)	Commercial		•		•			
MDL QSAR (MDL)	Commercial		•		•			
OASIS-TIMES (Laboratory of Mathematical Chemistry, Bourgas University)	Commercial	•						
OncoLogic (US EPA)	Freely available							
Pallas Suite including ToxAlert, Cytotoxicity (CompuDrug)	Commercial							
TerraQSAR (TerraBase)	Commercial		•					
TOPKAT (Accelrys)	Commercial	•	•		•	•		
Toxtree (JRC)	Freely available		•	•	•		•	
Molcode Toolbox (Molcode Ltd)	Commercial				•		•	
PASS	Freely available		•					