
Predictive Toxicology for Greener Chemicals
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UL | Empowering Trust in a Complex World

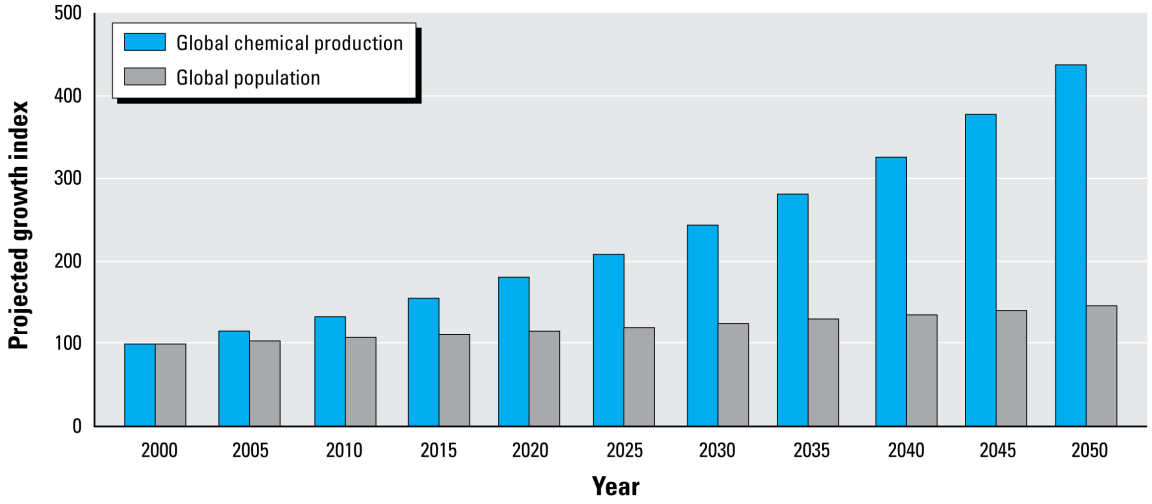
Global Chemical Market

>130x10^6
Chemical structures synthesized

140,000
Industrial chemicals used in global commerce

10,500
chemicals used in personal care products

4,500
Food Additives chemicals currently in use



Important data gaps may exist regarding chemical use and human & environmental health impact!

Chemical Compliance Pressures are Increasing

Dramatic increases in safety testing due to European REACH Registrations

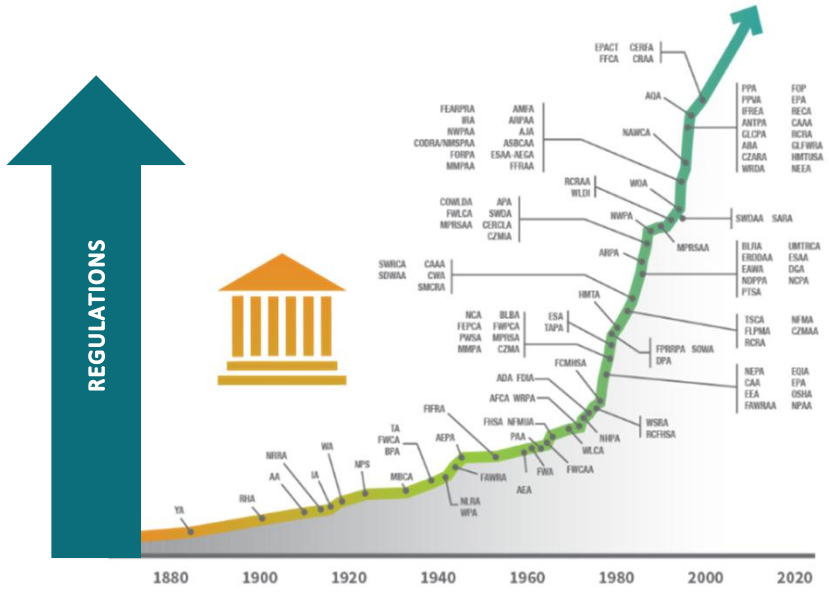
- 2010 & 2013 → testing proposals
- May 2018 → full submissions
- ≥ 30,000 chemicals

New or changing regulations

- Korea-REACH, Taiwan-REACH, China-REACH
- Lautenberg Chemical Safety Act (new TSCA)

Other assessment/testing needs

- Endocrine disruptors
- Mixtures
- Nanomaterials….



Chemical Sustainability Compliance Pressures are Increasing

- chemicals alternatives assessment (CAA) to substitute for the use of hazardous chemicals in products.
- >100 tools for comparing hazard characteristics of different chemicals.
- selection of alternatives for:
  - banned or restricted chemicals or materials;
  - chemicals that are perceived as hazardous by the public;
  - developing environmentally preferred products.

TABLE 3 GreenScreen® Hazard Assessments

CHEMICAL NAME & CAS#	Group I Human Health					Group II and II* Human Health									Ecotox		Fate		Physical	
	Carcinogenicity	Mutagenicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
							s	r*	s	r*										
Benzyl alcohol 100-51-6	L	L	L	M	DG	M	DG	L	M	H	H	DG	L	H	L	L	vL	vL	L	L
Caprylohydroxamic acid 7377-03-9	DG	L	DG	L	DG	L	DG	M	DG	DG	L	DG	L	H	H	H	vL	vL	L	L
Caprylyl glycol 1117-86-8	L	L	L	L	DG	L	DG	L	M	L	L	DG	L	H	H	M	vL	vL	L	L
DMDM Hydantoin 6440-58-0	H	M	L	L	DG	L	M	L	DG	DG	M	M	M	L	H	M	vL	vL	L	L
EDTA 60-00-4	L	L	L	M	DG	L	M	H	DG	DG	L	DG	M	H	H	H	M	vL	L	L
Ethylhexylglycerin 70445-33-9	L	L	M	L	DG	M	M	M	DG	L	M	DG	L	vH	M	M	M	vL	L	L
Gluconolactone 90-80-2	L	L	L	L	DG	L	L	L	DG	DG	L	DG	L	L	L	L	vL	vL	L	L
IPBC 55406-53-6	L	L	M	M	M	H	DG	H	M	L	H	DG	L	vH	vH	vH	L	vL	L	L

Name of method/tool	Tools that are designed to identify and screen out hazardous chemicals	Tools that are designed to compare alternatives	Tools that are designed to identify preferred chemicals and products
PRIO			
Quick Scan			
RISCTOX			
US EPA screening tools			
AAFA RSL			
GC3 RSLs			
Boots PSL			
SIN (Substitute It Now!) List			
Greenlist™			
GreenWERCS™			
SciVera Lens™			
3E GPA™			
IHS Greening Solutions			
Actio Material Disclosure			
DfE CAA			
Green Screen			
P2OASys			
Column Model			
CleanGredients			
Eco-Labels and Certifications			
Cleaner Solutions Database			
iSUSTAIN™			
BASF Eco-efficiency tool			
Skin Deep			

The new regulator

CHEMICAL SUPPLY CHAINS ARE COMPLEX

Green Chemistry
better ingredients

Alternative Assessments
innovate products

Hazard Communications
product safety (SDS)

Regulations
compliant products

Key Performance Indicators
sustainable products

Need for Hazard ata

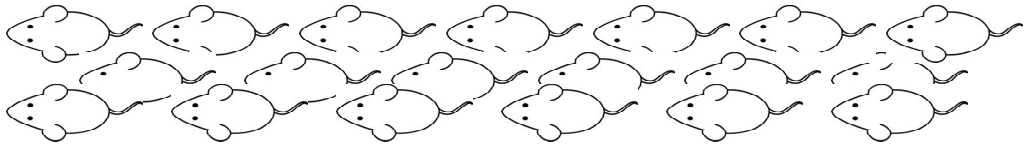
Can conventional toxicology approaches keep pace with the demands for chemical hazard data?

picture
© ChemSec

Conventional Toxicology

R&D → **Regulatory toxicology (e.g. REACH, EPA …)** → **Follow-up MoA (e.g. human relevance)**

Minimal involvement of Toxicologist in product design or selection

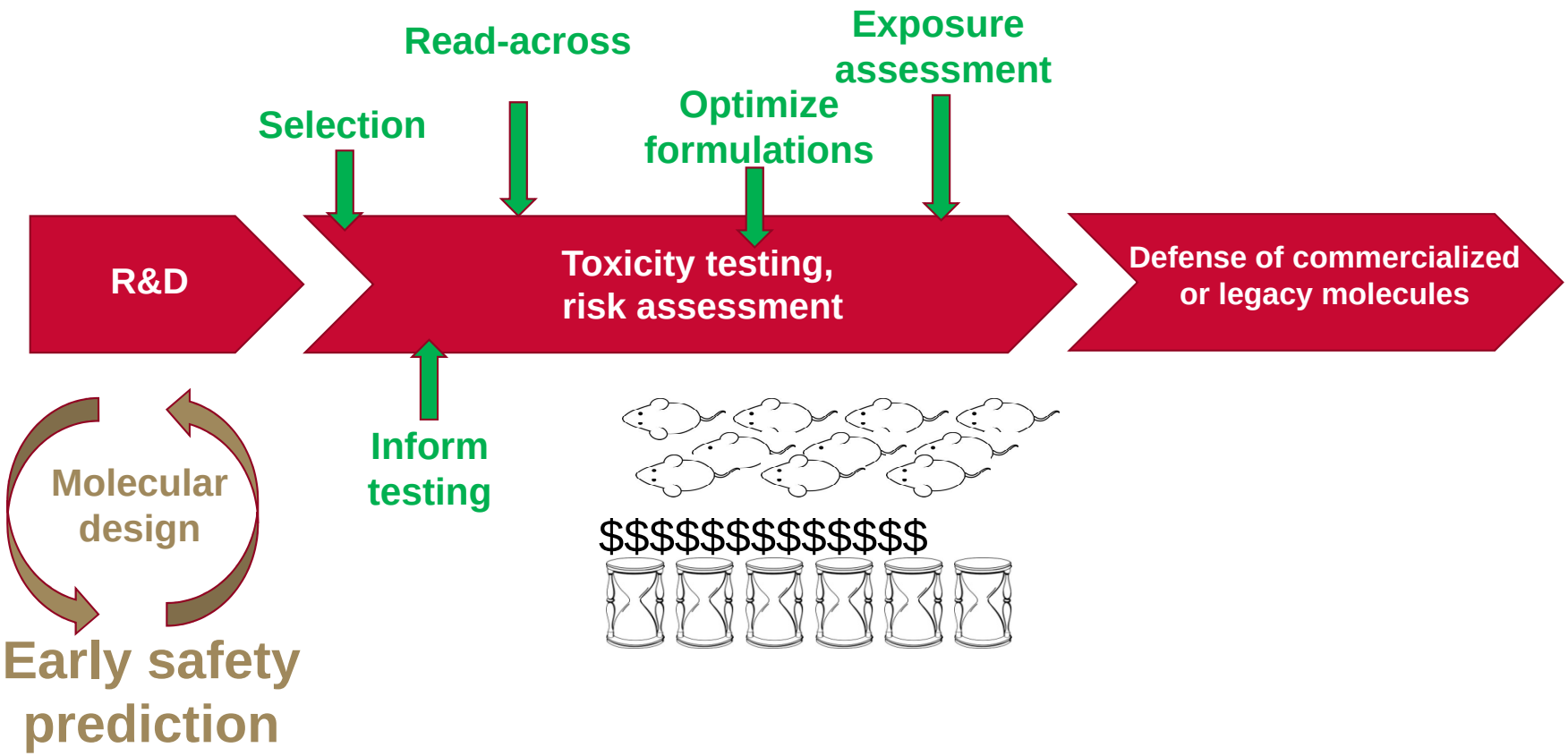


$$$$$$$$$$$$$$$$$$$$$$

Example - *Two-generation reproductive toxicity study:*

- ***Animal-intensive (>3,000 animals)***
- ***Expensive (>$500,000)***
- ***Slow (15 months)***

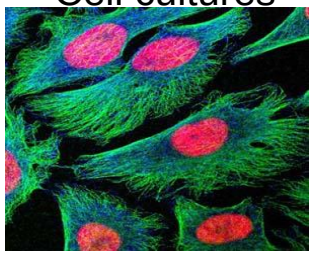
New Safety Assessment Paradigm



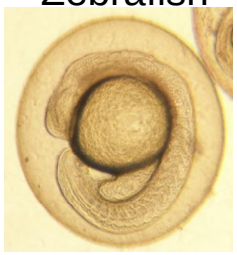
Predictive Toxicology Integrated Technology Platforms

In Vitro Biological Profiling

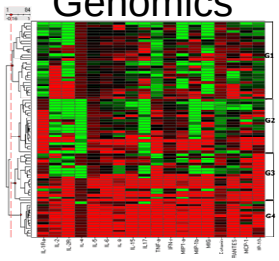
Cell cultures



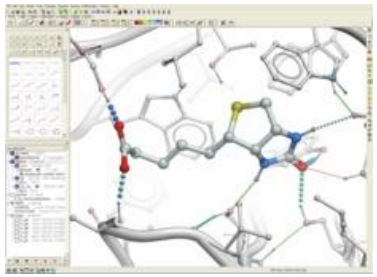
Zebrafish

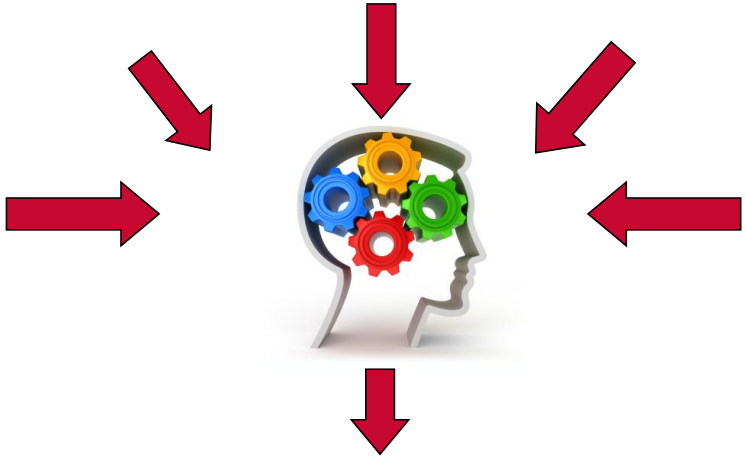


Genomics



Cheminformatics

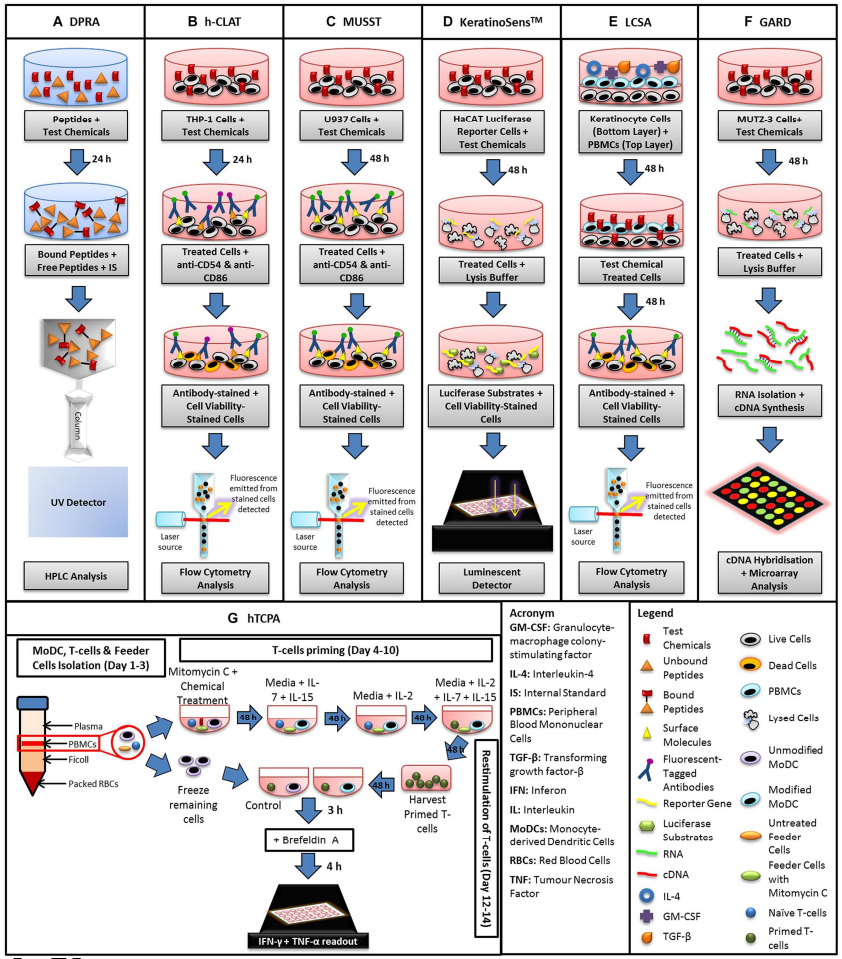




Exposure modeling

PREDICT SAFETY

Ex: Assays for Skin Sensitization*



Wong et al Front Pharmacol 6: 1-13, 2015

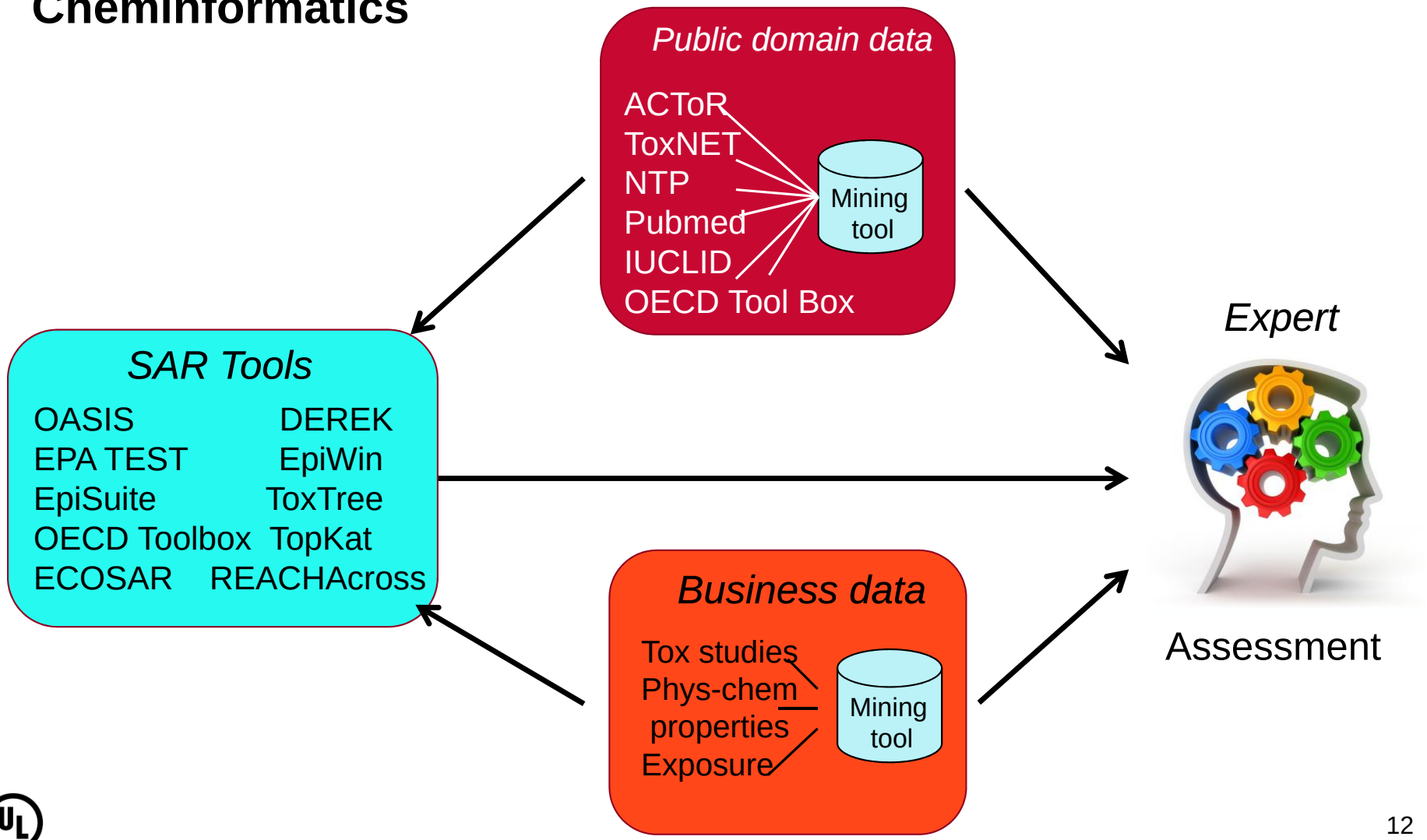
OECD Test Guidelines for in vitro Test Methods

Class	Test methods
Corrosion	In vitro Skin Corrosion: Transcutaneous Electrical Resistance Test Method (TER): TG430
	In vitro Skin Corrosion: Reconstructed Human Epidermis (RHE) test method: TG431
	CORROSITEX Skin Corrosivity Test: TG435
Skin irritation	In vitro Reconstructed Human Epidermis (RhE) Test methods, EpiDerm, EPISKIN, SkinEthic, LabCyte EPI-Model: TG439
Phototoxicity	3T3 NRU Phototoxicity Test: TG432
Eye irritation	Bovine Corneal Opacity and Permeability Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage: TG437
	Isolated Chicken Eye Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage: TG438
	Fluorescein Leakage Test Method for Identifying Ocular Corrosives and Severe Irritants: TG460
	Short Time Exposure In Vitro Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage: TG491
	Reconstructed human Cornea-like Epithelium (RhCE) test method for identifying chemicals not requiring classification and labelling for eye irritation or serious eye damage: TG492
Skin sensitization	In Chemico Skin Sensitization, Direct Peptide Reactivity Assay (DPRA): TG442C
	In Vitro Skin Sensitization, ARE-Nrf2 Luciferase Test Method: TG442D
Endocrine activity screening	Performance-Based Test Guideline for Stably Transfected Transactivation In Vitro Assays to Detect Estrogen Receptor Agonists and Antagonists: TG455
	H295R Steroidogenesis Assay :TG456
	BG1Luc Estrogen Receptor Transactivation Test Method for Identifying Estrogen Receptor Agonists and Antagonists: TG457
	Performance-Based Test Guideline for Human Recombinant Estrogen Receptor (hrER) In Vitro Assays to Detect Chemicals with ER Binding Affinity: TG493
Genotoxicity	Bacterial Reverse Mutation Test : TG471
	In vitro Mammalian Chromosome Aberration Test: TG473
	In Vitro Mammalian Cell Gene Mutation Tests using the Hprt and xprt genes: TG476
	In vitro Micronucleus Test: TG487
	In Vitro Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene: TG490
Skin absorption	Skin Absorption: In vitro Method: TG428

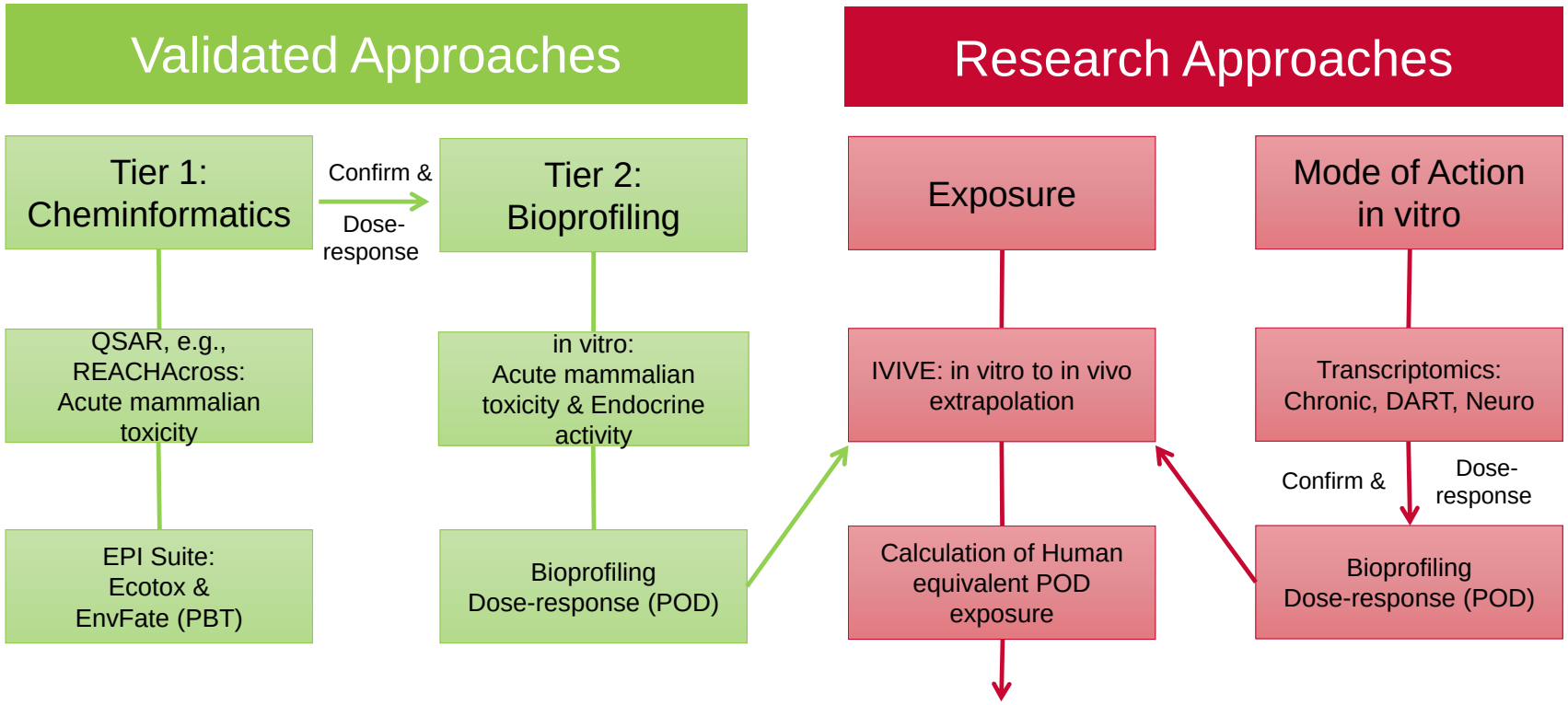
Cheminformatics QSAR methodologies have been developed

- Cheminformatics is the integration of all relevant information on a compound and its structural or substructural analogs in order to make a preliminary assessment of potential toxicity
  - **Statistical** – Predictions are made using a multilinear regression models fit to the training set using an algorithm-based approach.
  - **Mechanistic**- Predictions are made using a multilinear regression model for toxicity modes of action associated with specific chemical features.
  - **Nearest neighbor method** – The predicted toxicity is estimated by taking an average of a predefined number of chemicals in the training set that are most similar to the test chemical.
  - **Consensus method** – The predicted toxicity is estimated by taking an average of the predicted toxicities from each of the above QSAR methodologies.

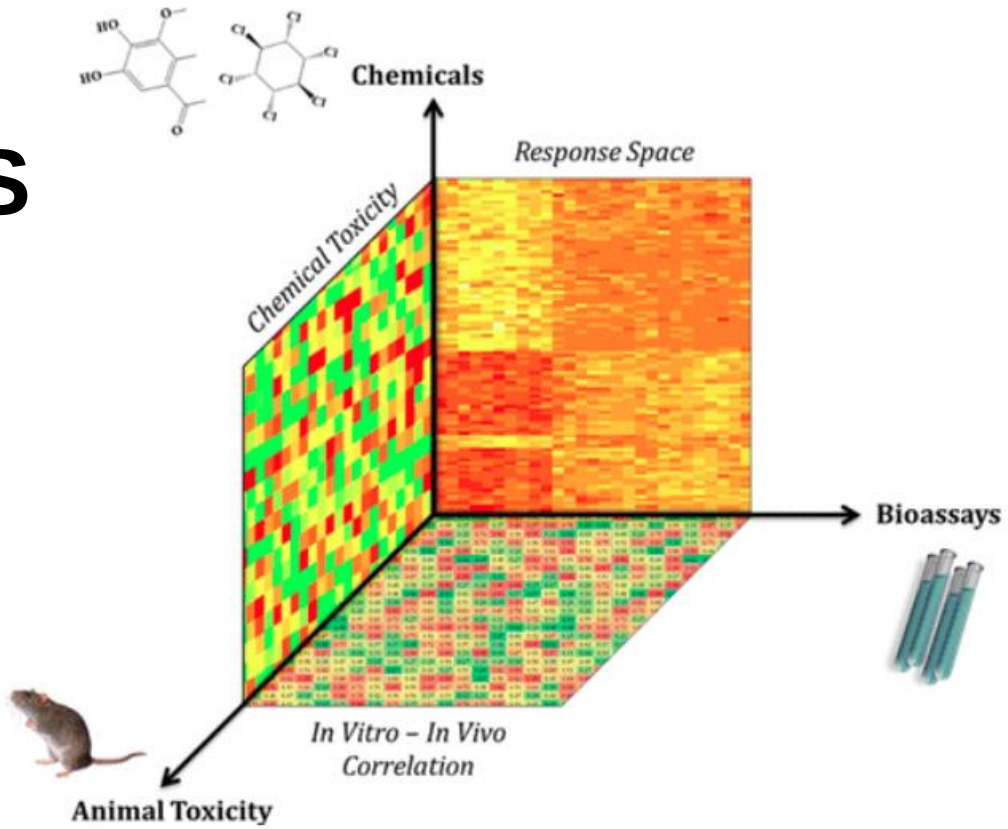
Cheminformatics



Integrated Non-animal Testing Strategy: New and Existing Chemicals

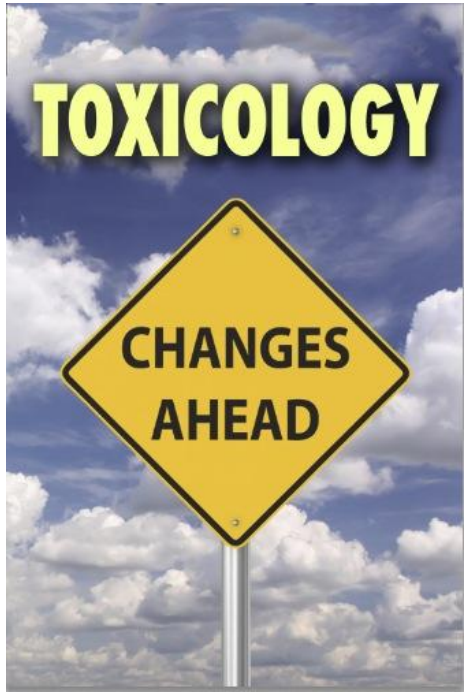


THE OPPORTUNITY OF BIG DATA & CHEMINFORMATICS



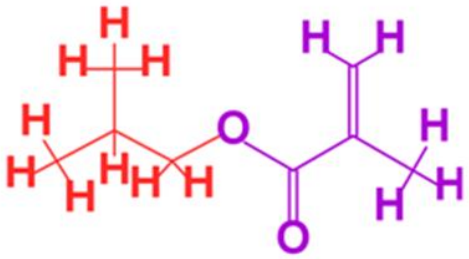
Big Data – Rapid Increase in Availability of Chemical and Toxicology Data

ECHA	Over 20,000 compounds	Animal & in vitro toxicity data
EPA	Over 2,000 compounds	Animal & in vitro toxicity data
EFSA	Close to 10,000 compounds	Animal & in vitro toxicity data
PubChem(27, 28)	Around 47 million compounds, over 700 000 bioassays, over 13 billion data points	Toxicity, pharmaceutical, genomics, and literature data
ChEMBL(87)	Over 600 000 compounds, 3.3 million bioassay readout data	Literature data
ACToR(88, 89)	The toxicity results from 100 various data resources	Both *in vitro* and *in vivo* toxicity data
ToxNET(90)	Over 50 000 environmental compounds from 16 different resources	Both *in vitro* and *in vivo* toxicity data
SEURAT(91)	Over 5500 cosmetic-type compounds in the current COSMOS database web portal	Animal toxicity data
CTD(37-40)	Over 13 000 compounds, over 32 000 genes, over 6000 diseases	Compound, gene, and disease relationships
CEBS(35)	About 10 000 toxicity bioassays from various sources	Gene expression data
DrugMatrix(92)	About 600 drug molecules and 10 000 genes	Gene expression data
Cmap(93)	About 1300 compounds and 7000 genes	Gene expression data



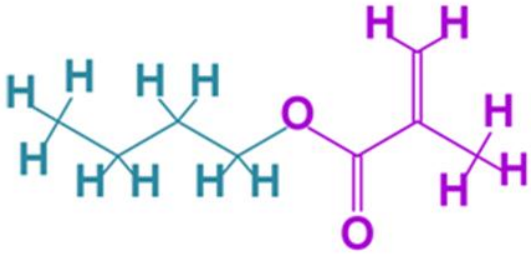
Comparing Chemicals to Establish Structural Similarities

Isobutyl Methacrylate



← 90% →

Butyl Methacrylate



0 1 0 0 1 1 0

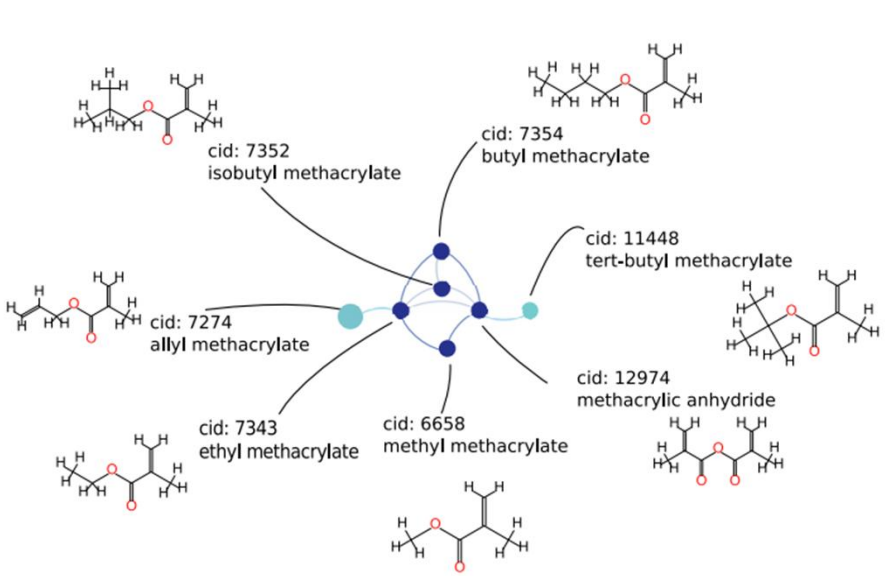
0 0 1 0 1 1 0

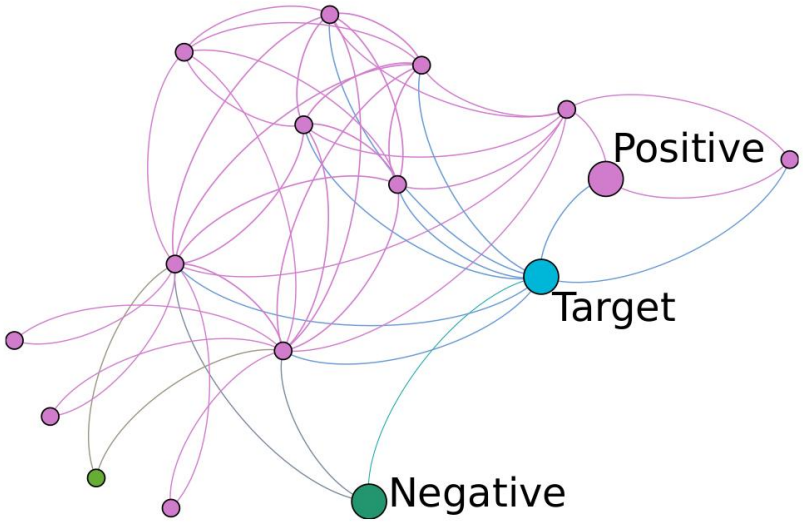
Vector (binary descriptor)
2D Conformational
Substructure Fingerprints

$$\frac{|A \cap B|}{|A| + |B| - |A \cap B|}$$

Tanimoto - Heuristic

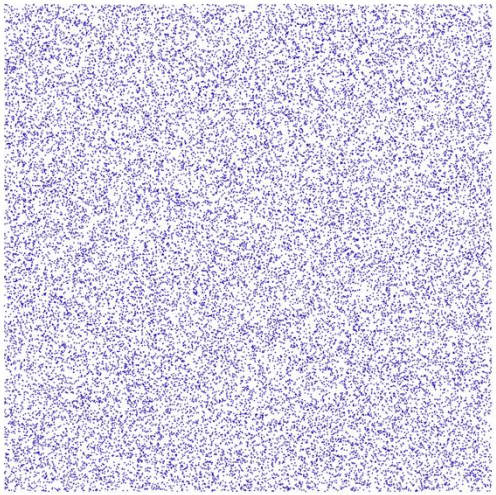
Hazard Predicted by Nearest Neighbor



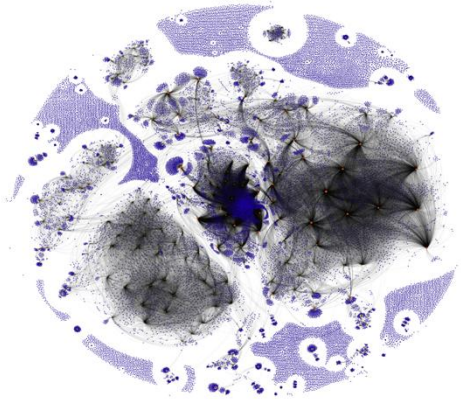


Increasing “Similars” with adding new Chemicals

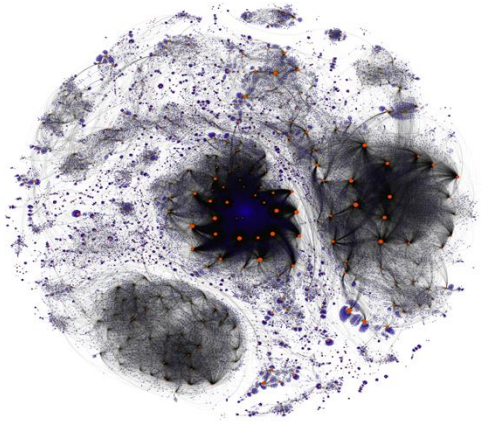
33383 Unlabeled Chemicals



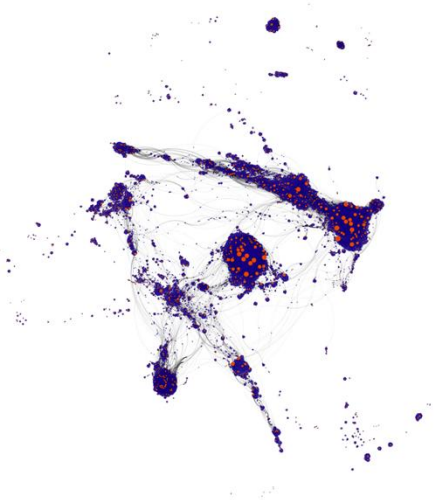
Similarity Map to 300 Labeled Chemicals



Similarity Map to 600 Labeled Chemicals



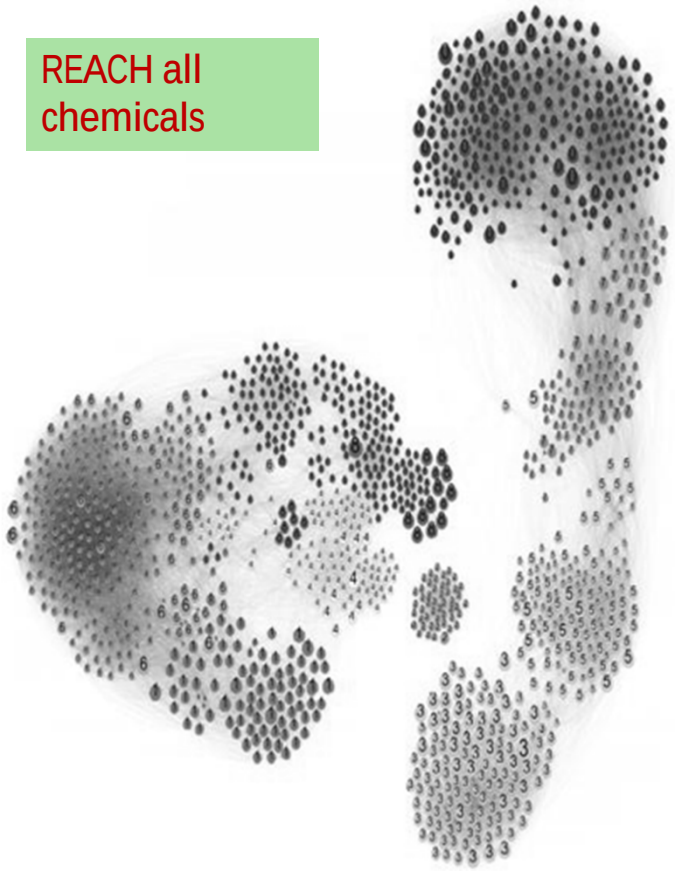
Similarity Map to 1387 Labeled Chemicals



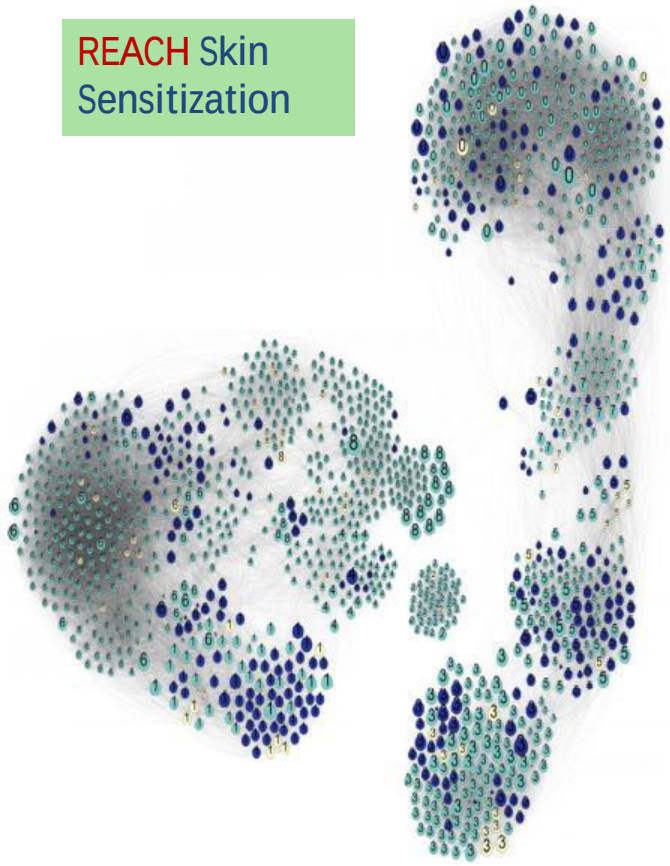
Network Connections → Increasing Information

Chemical Similarity

REACH all chemicals



REACH Skin Sensitization



UL REACHAcross™ Internal Validation

Accuracy similar to animal test

Nine endpoints: REACH 2018 <10 tons/a

Internal validation for unprecedented number of chemicals

Correctly Identified: True Positives, True Negatives

Average Se + Sp

Animal Studies

Endpoint	Total	Pos	Neg	Se%	Sp%	BAC%	BAC%
Acute Toxicity-Oral	12157	10225	1932	77	77	77	92
Acute Toxicity-Dermal	6314	4334	1980	77	75	76	78
Acute Toxicity-Inhalation	6184	4812	1372	74	75	74	
Skin Sensitization	4751	2865	1886	79	63	71	84
Skin Irritation	15106	13758	1348	69	71	70	76
Eye Irritation	15722	14778	944	83	56	70	84
Mutagenicity	3395	600	2795	75	71	73	75
Acute Aquatic Toxicity	2043	1122	921	76	74	75	
Chronic Aquatic Toxicity	2805	2554	251	78	66	72	

Cheminformatics (e.g., QSAR) for Green Chemistry

Principles of Green Chemistry.

Criteria for a useful toxicology tool:

- Assess human health AND environmental end points
- Rapid
- Relatively inexpensive
- No test material required
- User friendly

Resources:

USEPA: Toxicity Estimation Software Tool (TEST) https://www.epa.gov/chemical-research/toxicity-estimation-software-tool-test
ECHA JRC Computational Tools: https://eurl-ecvam.jrc.ec.europa.eu/laboratories-research/predictive_toxicology/qsar_tools
UL REACHAcross: https://www.ulreachacross.com/


Thank you