One Size Doesn't Fit All: Tailoring Read-across Methodology for TSCA and Other Contexts

James W. Rice, Ph.D.

NIEHS SRP Risk e-Learning Webinar
May 23, 2018

GRADIENT

TSCA Overview

- Toxic Substances Control Act (1976)
  - Governs (non-food, non-drug) chemicals
  - Established "Inventory" of chemicals in commerce
  - Established notification requirements
    - Pre-Manufacturing Notice (PMN)
    - Significant New Use Notice (SNUN)
  - Limited testing and data requirements
  - Possibility of restriction of harmful chemicals

Image: Clemens Pfeiffer

Cray 1 Supercomputer released in 1976
5.5 tons; 160 million FLOPS

TSCA Overview

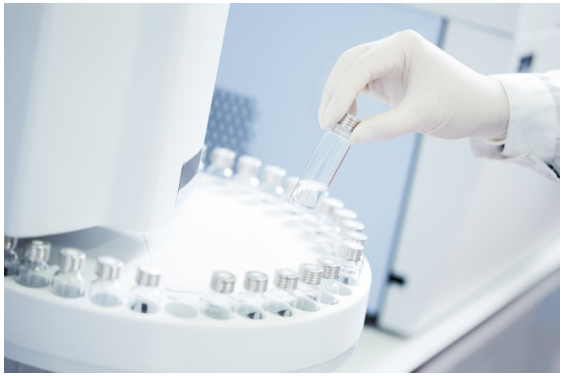
- Groundbreaking in 1976 but outmoded by the 2000s
  - EPA authority limited and passive (silence = approval)
  - Novel new materials (*e.g.*, nano)
  - Inventory outdated
  - Manufacturers facing variable regulations across the states
- 2016 Frank R. Lautenberg Chemical Safety for the 21st Century Act (LCSA)

Iphone 7 released in 2016
0.0002 tons (6.6 oz) vs. 5.5 tons
40 billion FLOPS vs. 160 million FLOPS

GRADIENT

TSCA Reform: Key Changes for New Chemicals

- EPA now has more authority to evaluate and manage chemical risks
- Requirement for **definitive determination** that chemical/use:
  - Presents unreasonable risk OR
  - May present unreasonable risk (more info needed) OR
  - Not likely to present unreasonable risk
- Overall, data requirements unclear!
- Prioritize non-vertebrate testing (Strategic plan June 2018)

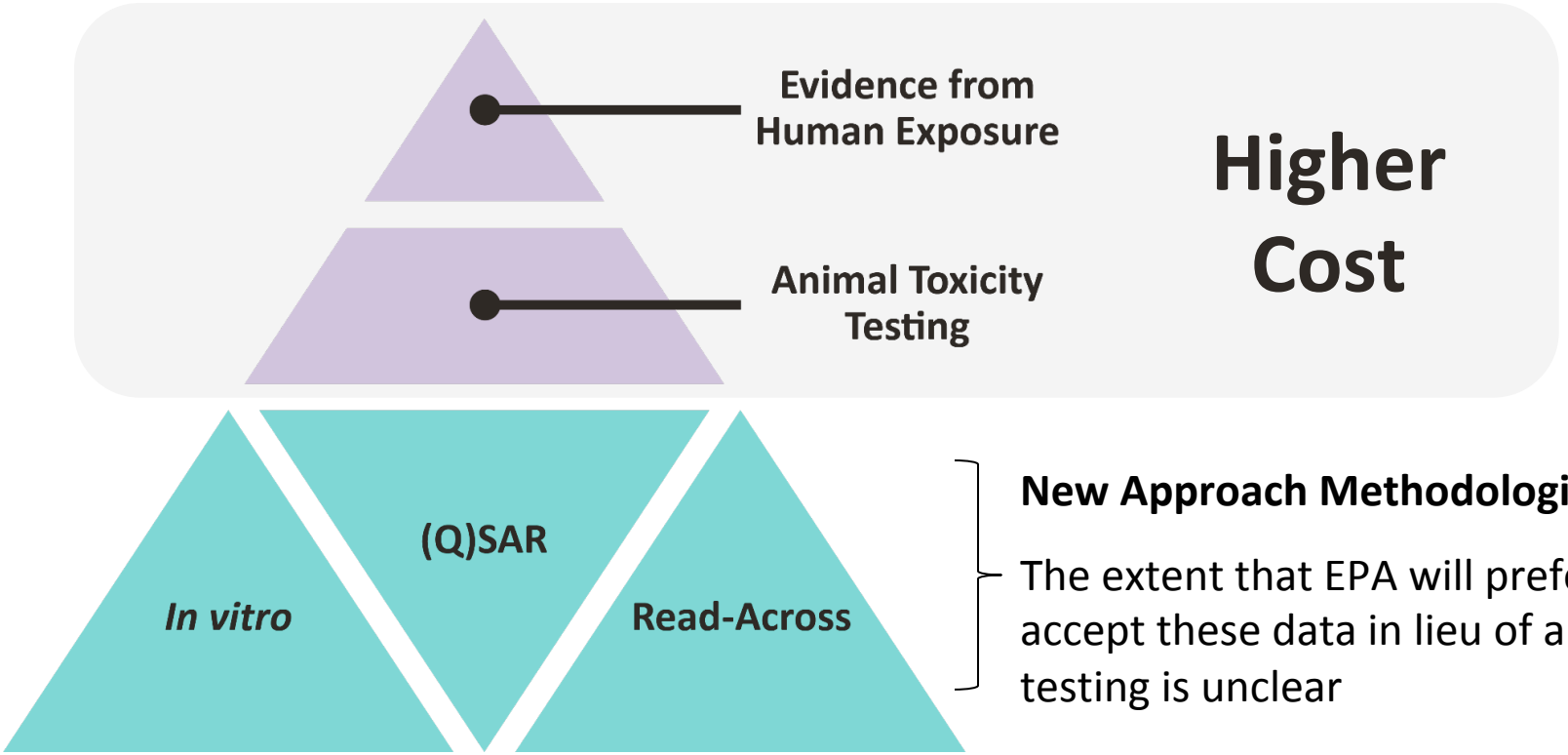


TSCA Reform: Key Changes for Existing Chemicals

- "Prioritization" of chemicals (high/low)
  - Only high chemicals require further risk evaluation
  - EPA must complete prioritization and designate 10 high and 20 low priorities by Dec. 2019
- Risk evaluation for (a few) high priority chemicals
  - 10 started in 2016 (from 2014 TSCA Work Plan); 10 more to begin no later than Dec. 2019
  - Unreasonable risks must be managed with use restrictions or other risk management measures

TSCA Reform: Impacts & Actions on New Data

- Must provide substantial data prior to chemical registration/sale
- Specifies science decisions must be "consistent with the best available science"



Animal Testing Isn't the Answer

- **Time consuming**
  - 90-day toxicity study can take over a year from planning to report
  - 2 year cancer bioassay takes up to 5 years
- **Expensive**
  - Full tox packages can cost millions
- **Wasteful/Ethically challenging**
  - Full tox packages will involve hundreds of animals
  - Most data will be similar to existing data for related chemicals
- **Imperfect**
  - Whole animal data require extrapolation, not always informative about *why* toxicity is occurring

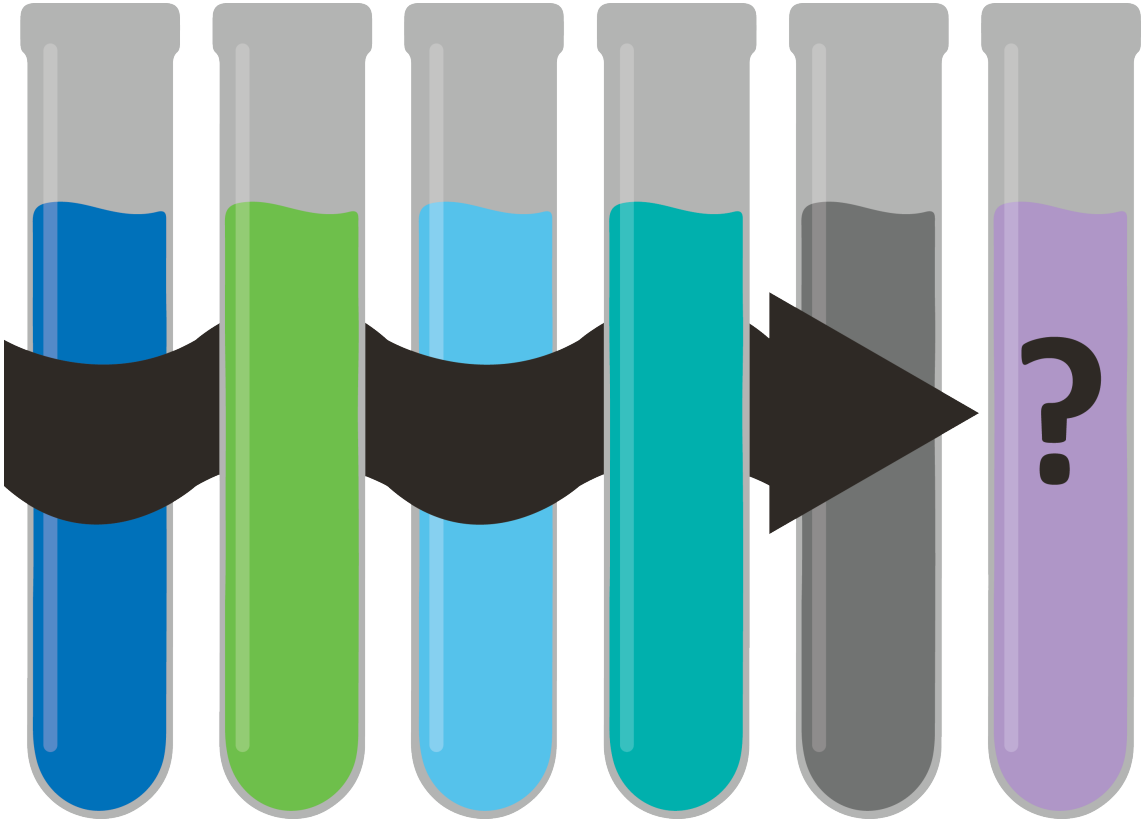
Challenges in Implementing New Methods

- **Need for Acceptance**
  - We are used to animal testing, the status quo
  - To avoid treating alternatives as add-ons rather than replacements
- **Challenges in Interpretation**
  - Is a cellular/molecular change adverse, pre-adverse, adaptive or normal?
- **Need for Standardization**
  - There are many alternative assays and programs, regulators can't know them all
- **Need for Flexibility**
  - Justification for use of alternative methods has to be context specific
  - Example: ECHA read-across guidance requires extensive justification, may not be appropriate for all situations where read-across is required

Decision Context is Important

- Product safety is more than chemical registration.
- Different applications may require different levels of effort and justification.
  - Drug/chemical discovery
  - Product impurity assessment
  - Alternatives assessment
- We developed and validated a read-across framework to fill dermal sensitization and irritation data gaps.

What Is Read-Across?

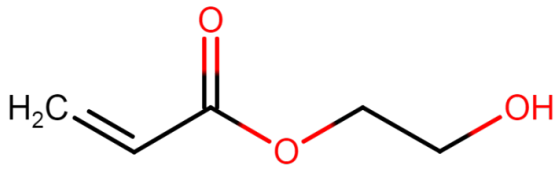


Properties of a known (data-rich) chemical, called a surrogate or analog, are "read across" to a new (data-poor) chemical

GRADIENT

Exploring the Utility of Endpoint-Specific Read-Across Tools – Case Study

Established a set of 28 chemicals with structural similarity to a target chemical: skin sensitizer **hydroxyethyl acrylate**



1. **Evaluated Chemical Structural Similarity**

2. **Considered Structure-Activity Relationship (SAR) Alerts**

3. **Determined Read Across Accuracy**

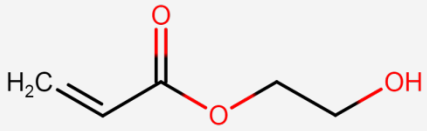
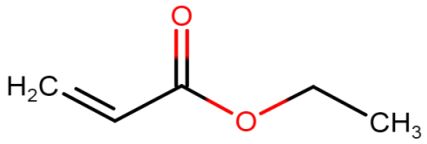
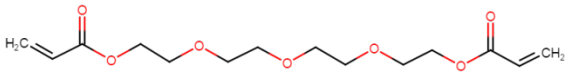
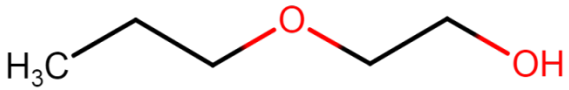
1. **Chemical Structural Similarity**
2. Structure-Activity Relationship (SAR) Alerts
3. Physicochemical Properties and Read-Across Accuracy

Evaluating Chemical Similarity

- ChemMine[a] and Toxmatch[b]
  - Used to explore and quantify similarity between the chemical structures of paired molecules
  - Enumerate structural features and subsequently calculate a Tanimoto coefficient[c]
  - Differences in methodology (*e.g.*, atom pair vs. molecular fingerprinting) can lead to discordant results

(a) Chemmine.ucr.edu; (b) European Commission Joint Research Centre;
(c) Proportion of structural features common to both compounds divided by the total number of features.

Chemical Similarity – Comparing Evaluation Tools

Compound of Interest	Structure	ChemMine Similarity Score	ToxMatch Similarity Score
Hydroxyethyl acrylate (target)		N/A	N/A
Ethyl acrylate		0.44	0.83
Tetraethylene glycol diacrylate		0.10	0.66
Ethylene glycol monopropyl ether		0.14	0.39

- Despite variation in similarity score value, the similarity rank order determined by ChemMine and Toxmatch demonstrated agreement.
  - Kendall's coefficient of concordance, W = 0.72, p = 0.067

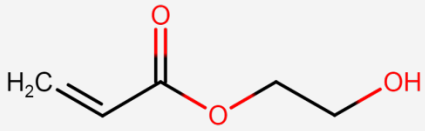
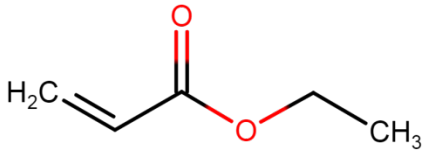
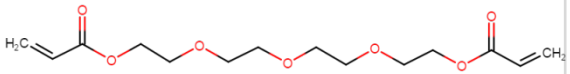
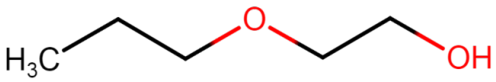
1. Chemical Structural Similarity

2. **Structure-Activity Relationship (SAR) Alerts**

3. Physicochemical Properties and Read-Across Accuracy

SAR Sensitization Alerts

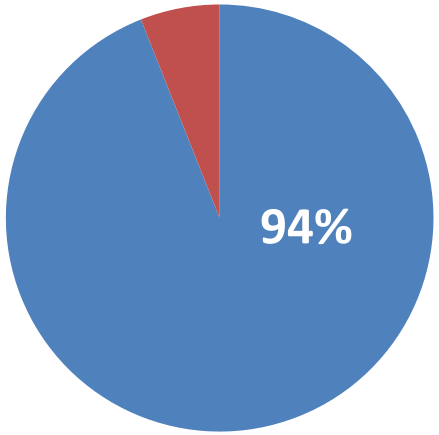
- Utilized two SAR programs - Toxtree and Derek Nexus™
- Compared results to animal test data

Compound of Interest	Structure	Toxtree SAR Alert?	Derek Nexus™ SAR Alert?	Animal Test Data
Hydroxyethyl acrylate (target)		Yes	Yes	Sensitizer
Ethyl acrylate		Yes	Yes	Sensitizer
Tetraethylene glycol diacrylate		Yes	Yes	Non-Sensitizer
Ethylene glycol monopropyl ether		No	No	Non-Sensitizer

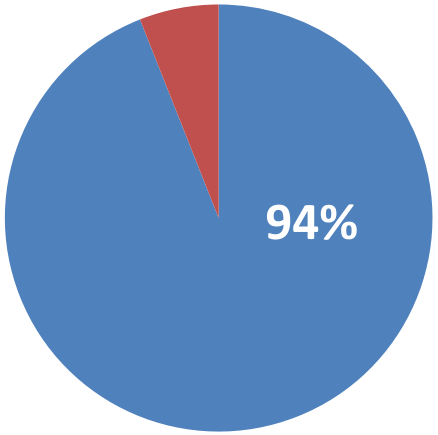
SAR Alerts – Comparing Evaluation Tools

- **True Positive Rate:**
  Hazard Present;
  Alert Present
- Hazard Present;
  Alert Not Present

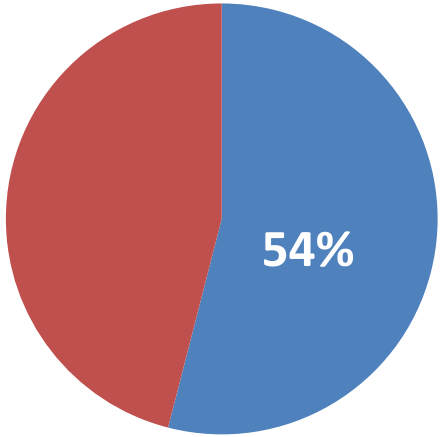
Toxtree

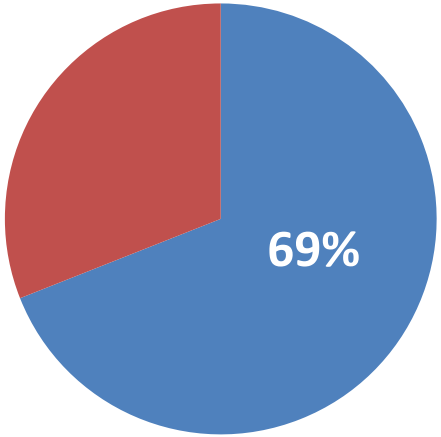


Derek Nexus™



- **True Negative Rate:**
  Hazard Not Present;
  Alert Not Present
- Hazard Not Present;
  Alert Present





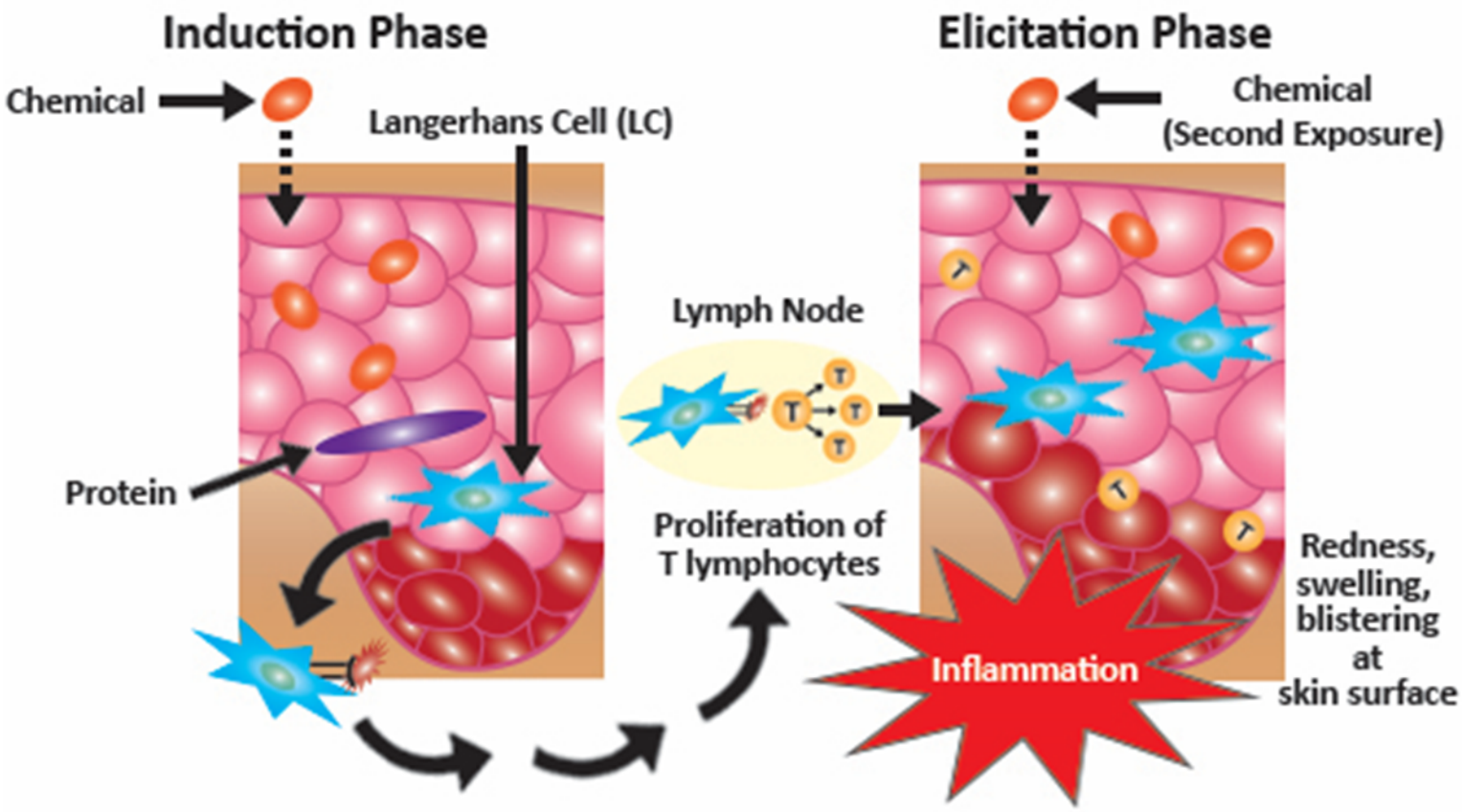
GRADIENT

1. Chemical Structural Similarity

2. Structure-Activity Relationship (SAR) Alerts

3. **Physicochemical Properties and Read-Across Accuracy**

Adverse Outcome Pathway for Skin Sensitization

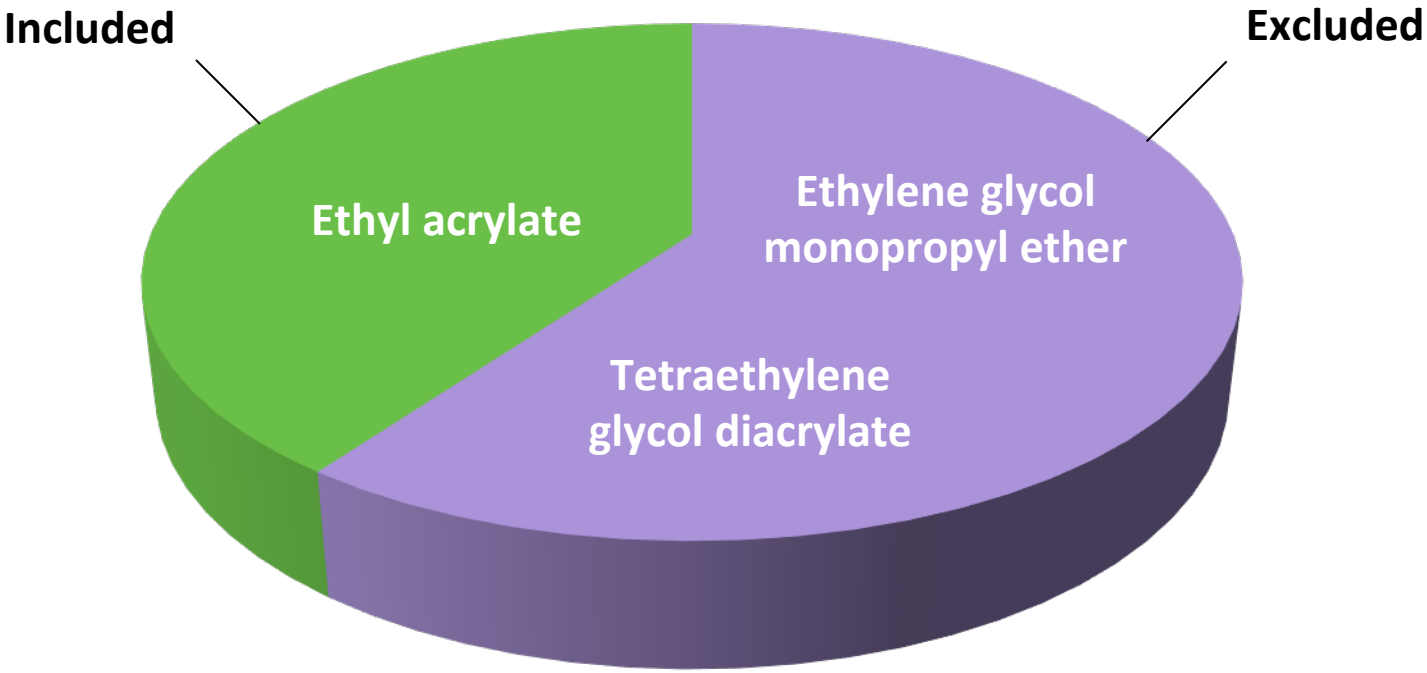


Exposure/Dermal Absorption based on chemical structure and properties

Physicochemical Property Exclusion Criteria

- Refined surrogate selection approach by considering physicochemical data and SAR alerts relative to target chemical
  - Molecular weight (excluded if greater than 2x that of target)
  - Aqueous solubility (excluded if less than 1/1000th of target)
  - Vapor pressure (excluded if greater than 2000x that of target)
  - ChemMine Similarity Score (excluded if less than 0.1)
  - SAR Alerts (include only those that trigger SAR alerts in both Toxtree and Derek Nexus™ - consistent with target)

Read-Across Accuracy



- Number of proposed surrogates decreased from 28 to 11
- Improved accuracy of read-across approach
  - Original test set: 15 out of 28 chemicals (54%) accurately matched hazard
  - Refined test set: 11 out of 11 chemicals (100%) accurately matched hazard

Conclusions and Future Work

- Endpoint-specific read-across can be used to bolster product safety evaluations when multiple tools and information sources are carefully implemented to fill data gaps.
- Robust chemical read-across is not necessarily one-size-fits-all.
- Agencies developing read-across guidance should consider that read-across approaches can be tailored to specific criteria and needs.
- Supporting case studies could be used justify read-across for TSCA (e.g., PMNs).

References and Resources

Backman, TW; Cao, Y; Girke, T. 2011. "ChemMine tools: An online service for analyzing and clustering small molecules." Nucleic Acids Res. 39(Web Server issue):W486-W491. doi: 10.1093/nar/gkr320.

Bjorkner, B. 1984. "The sensitizing capacity of multifunctional acrylates in the guinea pig. "*Contact Dermatitis* 11(4):236-246. doi: 10.1111/j.1600-0536.1984.tb00990.x.

Cohen, JM; Rice, JW; Lewandowski, TA. 2018. "Expanding the Toolbox: Hazard-Screening Methods and Tools for Identifying Safer Chemicals in Green Product Design." *ACS Sustainable Chem. Eng*. 6(2):1941-1950.

European Chemicals Agency (ECHA). 2016. "REACH dossier for 2-(propyloxy)ethanol (CAS No. 2807-30-9)." Accessed at https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/5863/1.

Ideaconsult Ltd. 2015. "Toxtree - Toxic Hazard Estimation by decision tree approach." Accessed at http://toxtree.sourceforge.net.

Ideaconsult Ltd. 2016. "Toxmatch." Accessed at https://eurl-ecvam.jrc.ec.europa.eu/laboratories-research/predictive_toxicology/qsar_tools/toxmatch.

Lhasa Ltd. 2016. "Derek Nexus." Accessed at https://www.lhasalimited.org/products/derek-nexus.htm.

National Library of Medicine (NLM) 2016. "ChemIDplus: A TOXNET database." Accessed at http://chem.sis.nlm.nih.gov/chemidplus/ .

GRADIENT

Thank you

jrice@gradientcorp.com

James W. Rice, Ph.D.
Gradient
20 University Road, Cambridge, Massachusetts, USA

www.gradientcorp.com
https://gradientcorp.com/working-at-gradient.html

GRADIENT