Optimizing the Evidence Integration Approach for Hazard Assessment for Chemicals with No Testing Data

Marisa Kreider, PhD, DABT

SCHC Fall Meeting, 2020

Intellectual Property Statement

The material contained in this presentation is the work of expert(s) selected by the Program Committee of SCHC and is intended solely for the purpose of professional development and continuing education. Material in an SCHC-sponsored presentation does not constitute a recommendation or endorsement of any kind. This material is believed to accurately represent current regulatory requirements and industry standards for hazard communication. However, SCHC cannot guarantee the accuracy or completeness of this information. Users are responsible for determining the suitability and appropriateness of these materials for any particular application.

Optimizing the Evidence Integration Approach for Hazard Assessment for Chemicals with No Testing Data

Marisa Kreider, Ph.D., DABT
Cardno ChemRisk, LLC

November 11, 2020

Outline

- Problems in Hazard Assessment for Industry
- Review of Tools Available for Hazard Assessment
  - Strengths and limitations
- Integrating Approaches
- Incorporating Assessments into Product Stewardship

What is Chemical Hazard Assessment?

Toxicological

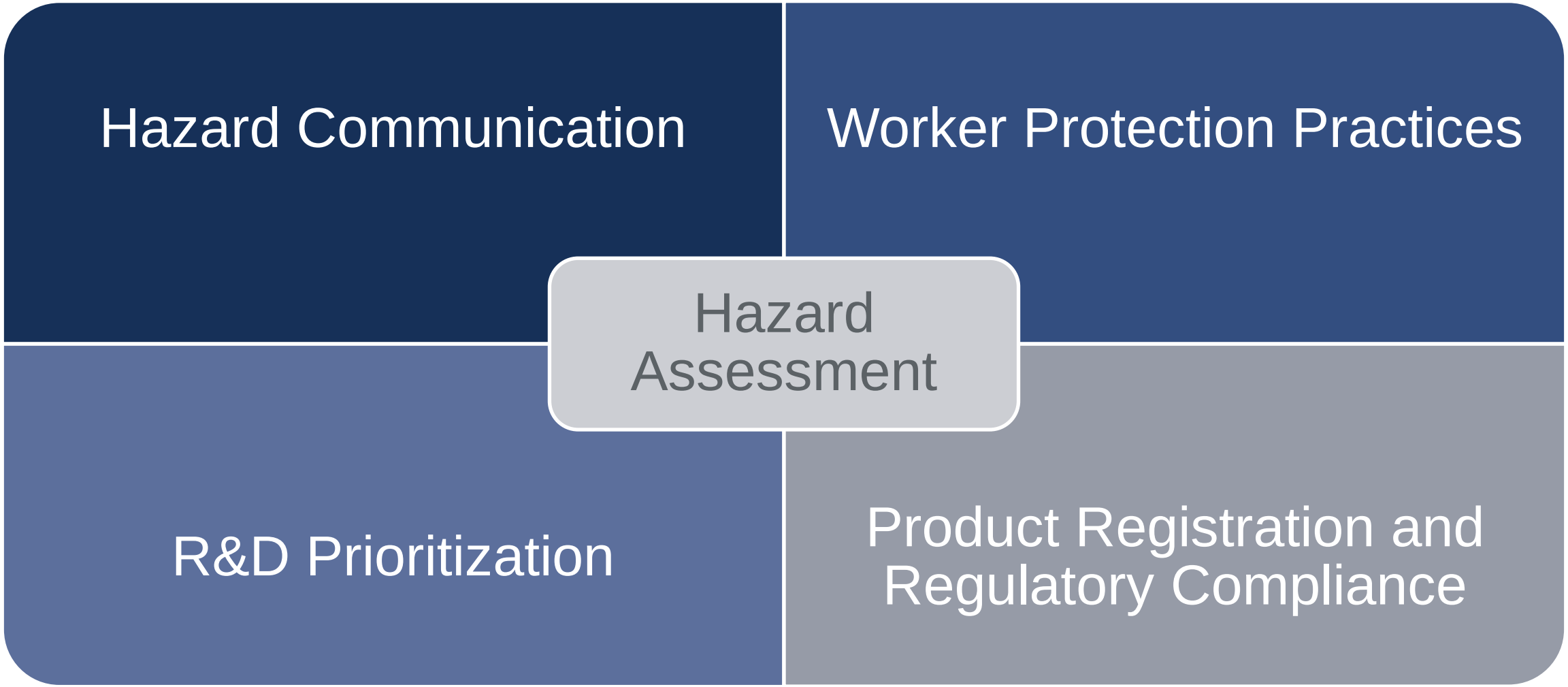
- Acute Toxicity/Lethality
- Target Organ Toxicity
- Carcinogenicity
- Mutagenicity
- Reproductive/Developmental Toxicity
- Irritation/Corrosion
- Sensitization

Physical

- Flammability
- Explosivity
- Corrosivity
- Oxidizers

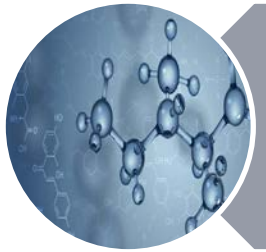
Cardno ChemRisk

Uses for Chemical Hazard Assessment



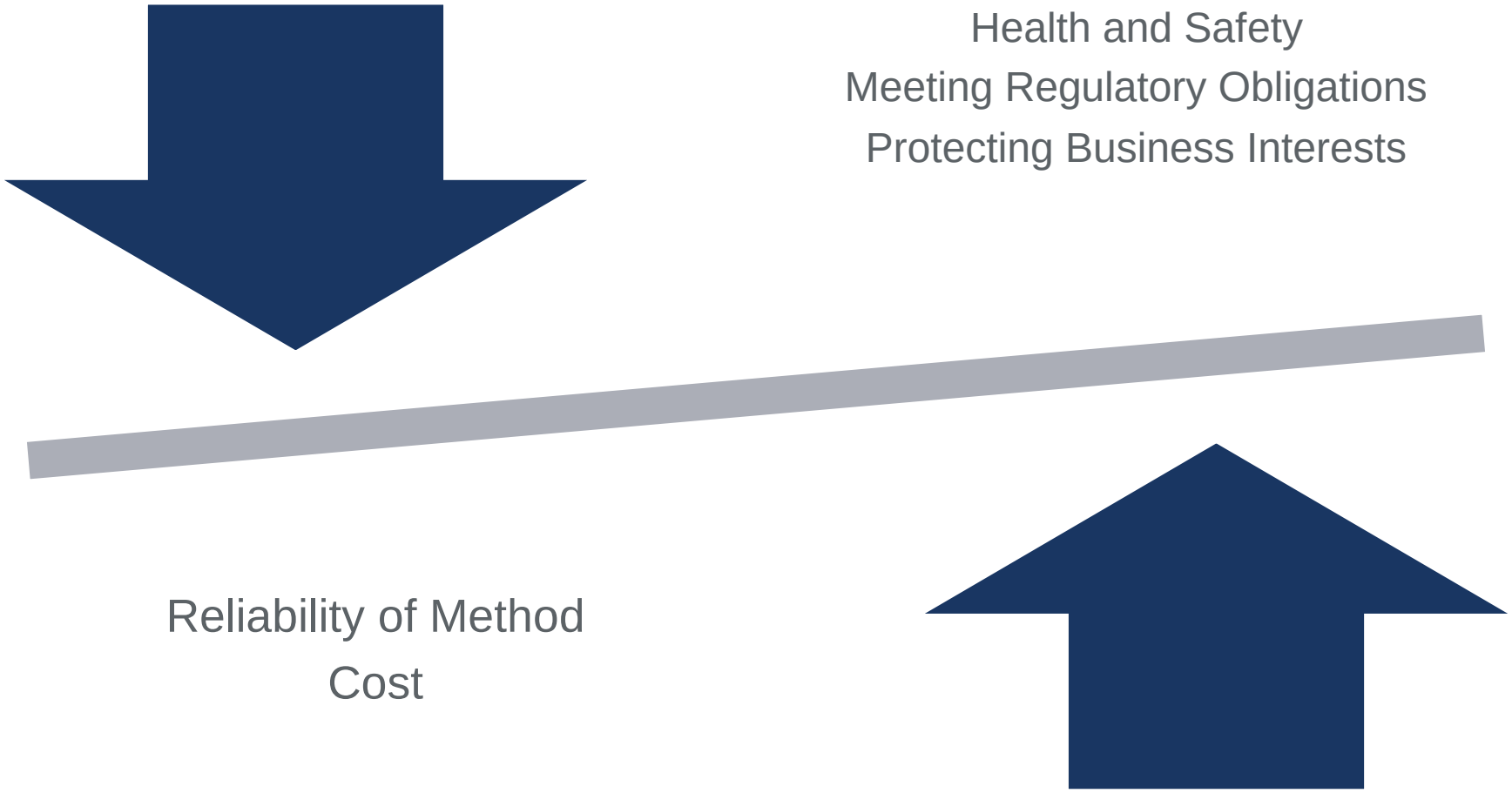
Cardno ChemRisk

How Can Companies Gather Information on Hazards?

Methods	Challenges
 Review Existing Literature or Available Information	Contingent on availability
 Conduct Testing	Potentially costly
 Use Predictive Methods	Rely on basic inputs but sophisticated interpretation

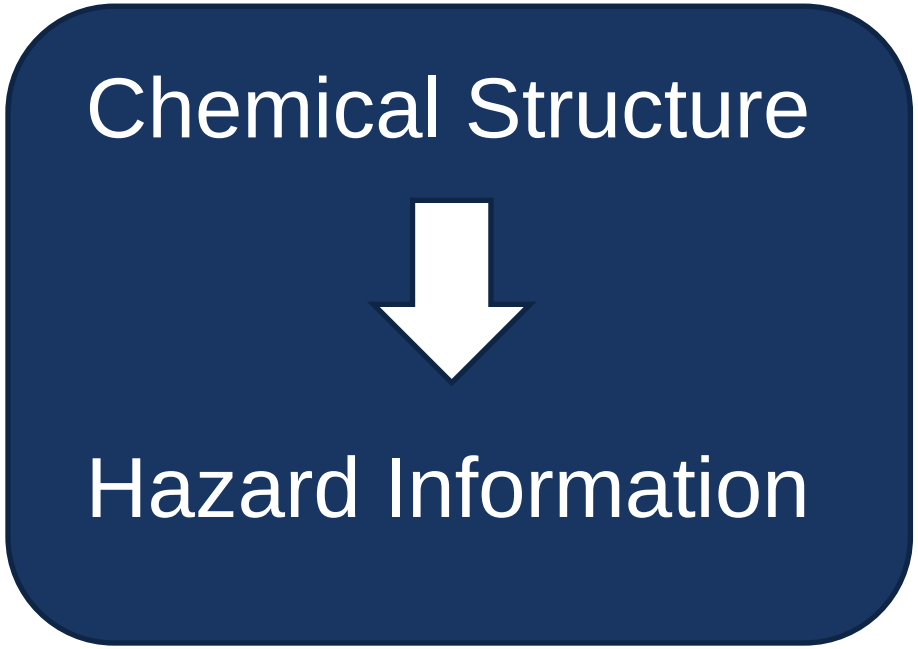
Cardno ChemRisk

A Delicate Balance



Computational Analysis for Hazard Assessment- A Growing Field

- Methods for hazard assessment have been developed to rely on structural information to inform potential hazards
- Increasingly popular due to:
  - Reduced reliance on animal testing
  - Regulatory promotion of alternate methods
  - Cost of empirical testing
- Example tools available:
  - Read-across and analog identification tools
  - (Quantitative) Structure Activity Relationships ([Q]SAR}
  - Metabolite predictors
  - Tools to provide ancillary information (e.g. phys-chem properties)



Cardno ChemRisk

Read-Across and Analog Identification

- Read-across relies on application of toxicity data from a chemical with a known toxicity profile to one without data
- Reliance on data for chemicals within a family or chemicals with similar structures and characteristics
  - Example: EPA Chemical Categories
- Tools to identify read-across candidates (a.k.a. analogs)
  - Analog Identification Methodology Tool (AIM; U.S. EPA)
  - ChemID Plus (NIH)

(Quantitative) Structure Activity Relationships

Rule-Based

- Structural Alerts
- Often based on known mechanisms of action
- Require less robust training of tool
- Typically cannot provide quantitative predictions

Statistically-Based

- Rely on mathematical models or machine learning
- Require robust training; care should be taken in interpretation of applicability
- Some can provide quantitative predictions

(Q)SAR Tools

- There are many….
- OECD QSAR Toolbox offers free one-stop shopping to cover many endpoints
  - Combines freely available software across a variety of agencies/providers into one tool
  - Also offers metabolism profiling options and analog ID
- Other endpoint specific software tools exist
  - Examples: Oncologic (mutagenicity/carcinogenicity), ECOSAR (ecotox), OASIS (sensitization)
- Proprietary/subscription software also exists
  - Examples: Derek Nexus, Sarah Nexus (LhasaLimited)

Integration Across Tools

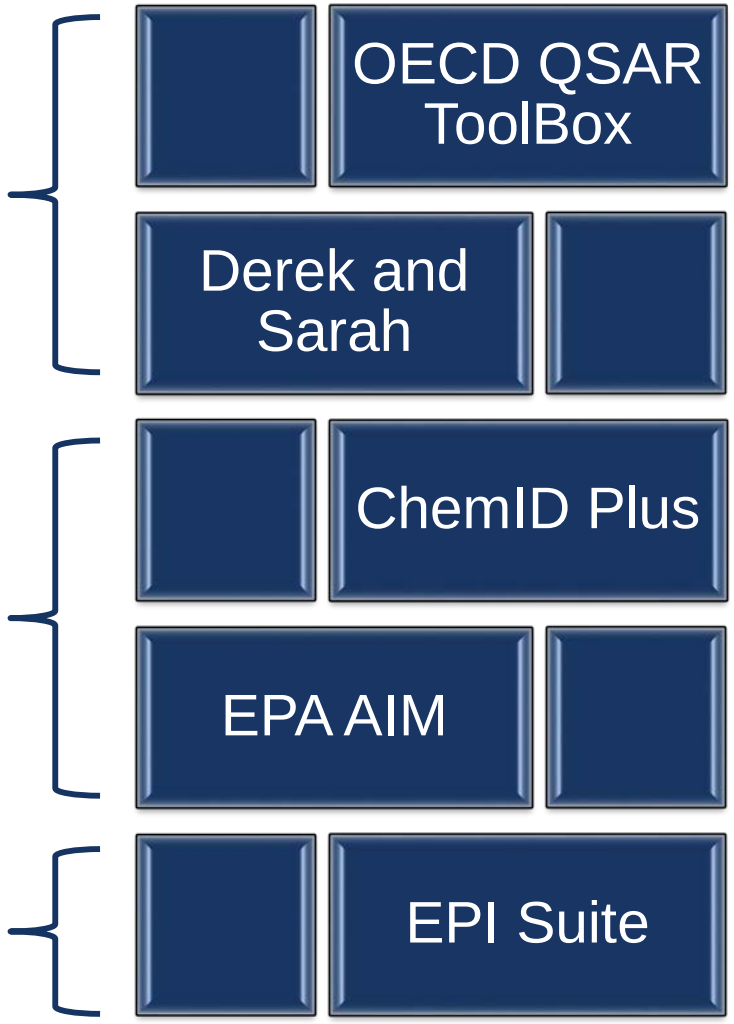
- No single tool is perfect– how can you combine tools to draw conclusions?
- General recommendations:
  - Rely on a multi-pronged approach, including read-across, QSAR, physical-chemical properties, etc.
  - When using QSAR, use both rule and statistically-based software packages
  - Look for consistency across tools
  - Consider potential metabolites or breakdown products (e.g. hydrolysis products)

Exemplar Framework

QSAR Tools, includes mixture of both rule and statistically based tools

Analog identification tools

Physical-Chemical Properties; used to inform pharmacokinetics



*All computational analyses supplemented with professional judgment to determine potential active moieties to be used in read-across and potential degradation products

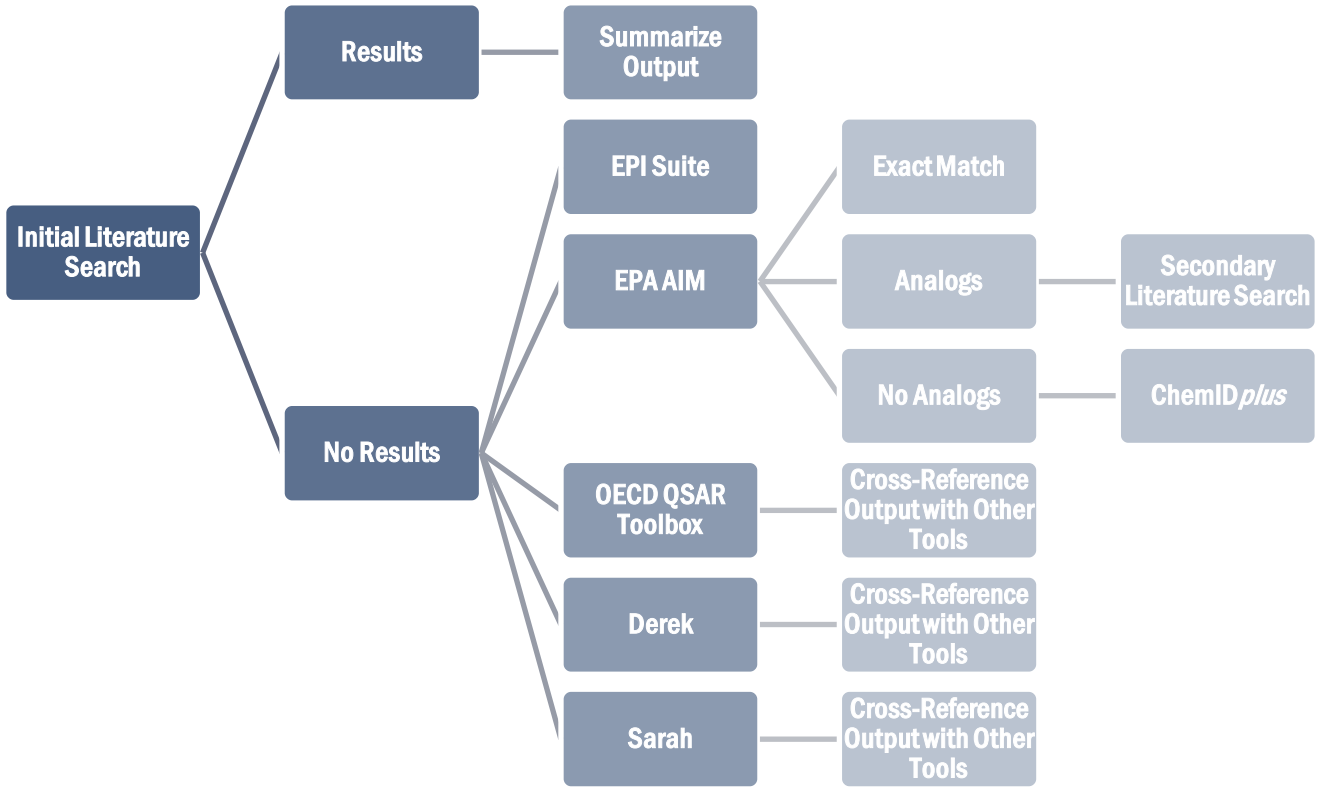
Cardno ChemRisk

Framework Coverage

Endpoint	OECD ToolBox	Derek	Sarah	EpiSuite	EPA AIM	ChemID Plus
Acute Toxicity	X	X				
Repeat Dose/Target Organ Toxicity	limited	X				
Skin and Eye Irritation	X	X				
Sensitization	X	X				
Genotoxicity	X	X	X (probabilistic)			
Cancer	X	X				
Reproductive and Developmental	X	X				
Ecotoxicity	X			X		
Toxicokinetics				indirectly		
Physical-Chemical Properties	X			X		X
Metabolites	X					
Analogs	X				X	X

Test Run of Framework

- Conducted test runs of chemicals with limited but available data using this approach
- Compared the data obtained from the framework with the test data when available
- Three chemicals:
  - Tetrabromobisphenol A diallyl ether (TBBPA DAE), CAS# 25327-89-3
  - Cyclemax, CAS# 7775-00-0
  - 2,2,2-trifluoro1-(trifluoromemethyl)ethyl methacrylate (HFIPMA), CAS# 3063-94-3



Cardno ChemRisk

What Do The Computational Tools Tell Us?

Endpoints		TBBPA DAE	Cyclemax	HFIPMA
Acute Toxicity	OECD	High (Class III) Cramer Toxicity	Low (Class I) Cramer Toxicity; Phenyl-substituted saturated and unsaturated aldehydes; U.S. EPA New Chemical Categories: Aldehydes	High (Class III) Cramer Toxicity; Methacrylic acid esters; US-EPA New Chemical Categories: Acrylates/ Methacrylates and Esters
Skin Irritation	OECD	Inclusion rules not met	Aldehydes	Inclusion rules not met
	Derek	No alerts found	No alerts found	Alert based on alpha,beta-unsaturated esters
Eye Irritation	OECD	Inclusion rules not met	Inclusion rules not met	Inclusion rules not met
	Derek	No alerts found	No alerts found	Alert based on alpha,beta-unsaturated esters
Sensitization	OECD	No alerts found	Category 1B Skin Sensitizer; Schiff base formation with carbonyl compounds	Protein binding by Michael addition; Respiratory sensitization by Michael addition
	Derek	Non-sensitizer	Alert based on aldehydes	Alert based on alpha,beta-unsaturated esters or precursors
Carcinogenicity	OECD	No alerts found	Aldehyde Type Compounds	Acrylate Reactive Functional Groups
	Derek	Plausible based on polyhalogenated aromatic alert	No alerts found	No alerts found
DART	OECD	Not known precedent reproductive and developmental toxic potential	Known precedent reproductive and developmental toxic potential p-tert-Butyl-alpha-methylhydrocinnamic aldehyde (BMHCA)-like chemicals (9a)	Not known precedent reproductive and developmental toxic potential
Genotoxicity/ Mutagenicity	OECD	No alerts found	DNA binding; Simple aldehyde	DNA binding
	Derek	Inactive in vitro in bacterium	Alert for non-specific genotoxicity, chromosome damage in vitro in mammal, and mutagenicity in vitro in mammal based on alkyl aldehydes; Inactive for mutagenicity in vitro in bacterium	Alert for chromosome damage in vitro in mammal based on alpha,beta-unsaturated ester or thioester; Inactive for mutagenicity in vitro in bacterium
	Sarah	Negative with 33% confidence	Negative with 49% confidence	Negative with 64% confidence

No alerts for: Repeat dose toxicity (either tool), acute toxicity (Derek), and DART (Derek)

How Do You Interpret Across Lines of Evidence?

- Tools can offer multiple outcomes, including positive and negative (no alerts, or not [hazardous]), not categorizable, outside domain of positive (e.g. inclusion rules not met)– all of these terms mean slightly different things
- Reliability of the prediction depends on consistency of the tool and strength of the conclusion
  - If there are alerts with multiple tools, this strengthens the conclusion
  - If there is an alert with one tool, but not another– this may weaken the conclusion (depending on the type of statement)
- Our approach is to default to positive, if at least one tool predicts that effect occurs with the chemical of interest
  - Modify the strength of that conclusion based on consistency across tools and any other relevant factors (e.g. chemical shape and potential for accessibility of structural components)

Interpretation Across Tools for Each Chemical

- Example with TBBPA DAE:
  - Acute Toxicity: Positive alert in OECD, based on lack of specific structural alignment with low toxicity classes- Positive with low reliability
  - Irritation (skin and eye): No alert/did not meet inclusion rules for either tool- Negative with moderate reliability
  - Sensitization: No alerts (OECD) and specific statement of “non-sensitizer” (Derek)- Negative with moderate/high reliability
  - Carcinogenicity: Conflicting results (No alert in OECD; plausible statement in Derek based on polyhalogenated aromatic structure)- Positive with low reliability
  - DART: No alerts/no known precedent for across both tools- Negative with moderate reliability
  - Mutagenicity/Genotoxicity: No alerts and/or negative across all three tools; Sarah predicted negative with 33% confidence- Negative with moderate/high reliability

What Does the Empirical Data Tell Us?

	TBBPA DAE	Cyclemax	HFIPMA
Acute Toxicity (oral)	LD50 > 5000 mg/kg bw	LD50 > 2000 mg/kg bw	LD50 >2000 mg/kg bw
Repeated Dose Toxicity	No information	No information	No information
Skin Irritation	Not classified as a skin irritant	Category 2 Skin Irritant	Not classified as corrosive
Eye Irritation	Not classified as an eye irritant	Not classified as an eye irritant	Not classified as an eye irritant
Sensitization	No information	Category 1B Skin Sensitizer	No information
Carcinogenicity	No information	No information	No information
DART	No information	Decreased sperm count at >=75 mg/kg bw Microscopic changes in testis and epididymis and decreased sperm quality at 300 mg/kg bw	No information
Genotoxicity/Mutagenicity	Negative for mutagenic activity	Negative for mutagenic activity	No information

How Does the Empirical Data Compare to Tools?

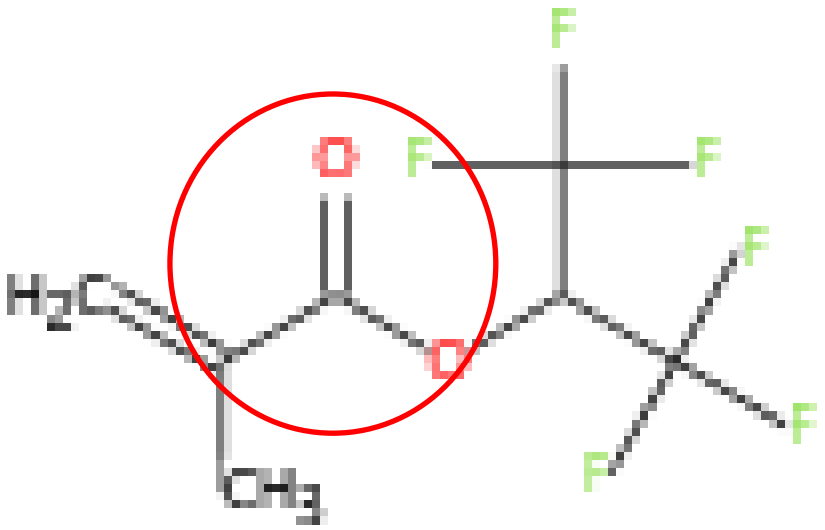
	TBBPA DAE	Cyclemax	HFIPMA
Acute Toxicity (oral)	LD50 > 5000 mg/kg bw	LD50 > 2000 mg/kg bw	LD50 >2000 mg/kg bw
Repeated Dose Toxicity	No information	No information	No information
Skin Irritation	Not classified as a skin irritant	Category 2 Skin Irritant	Not classified as corrosive
Eye Irritation	Not classified as an eye irritant	Not classified as an eye irritant	Not classified as an eye irritant
Sensitization	No information	Category 1B Skin Sensitizer	No information
Carcinogenicity	No information	No information	No information
DART	No information	Decreased sperm count at >=75 mg/kg bw Microscopic changes in testis and epididymis and decreased sperm quality at 300 mg/kg bw	No information
Genotoxicity/Mutagenicity	Negative for mutagenic activity	Negative for mutagenic activity	No information

Yellow = Inconsistent with Tool
Green = Consistent with Tool
Gray = No comparison possible

Cardno ChemRisk

Why Are Predictions for HFIPMA Inconsistent with Data?

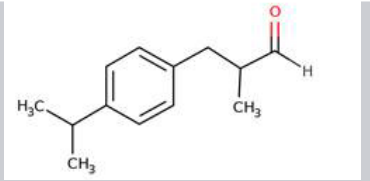
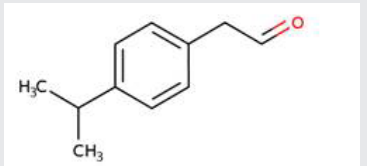
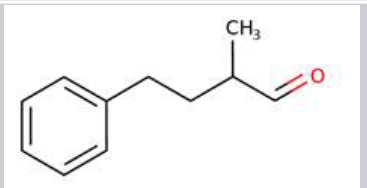
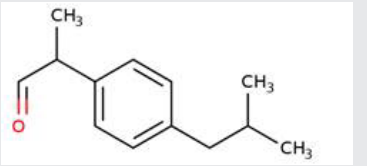
- Skin and eye irritation prediction for HFIPMA are based on presence of alpha and/or beta-unsaturated esters
- Accessibility of these esters may be hindered by larger structures present in HFIPMA



Cardno ChemRisk

What Do Analogs Tell Us?

- Analogs only identified for Cyclemax
- Analysis of analogs using computational tools and empirical data indicate the analogs are also skin irritants, skin sensitizers, and are Class I for acute toxicity

	CAS Number	Structure	Known Hazards
Hydrocinnamaldehyde, p-isopropyl-alpha-methyl-	103-95-7		Skin irritant Skin sensitizer
Acetaldehyde, (p-isopropylphenyl)-	4395-92-0		Unknown
Benzenebutanal, alpha-methyl-	40654-82-8		Cramer Class I Acute Toxicant
2-[4-(2-Methylpropyl)phenyl] propanal	51407-46-6		Unknown

Cardno ChemRisk

Other Tools

- EPISuite can inform relevant routes of exposure and potential for bioaccumulation based on physical-chemical properties
- For example, TBBPA DAE has a very low vapor pressure, poor water solubility, and a high bioconcentration factor
  - Therefore, unlikely to result in significant exposure via inhalation; likely to partition to fat in body, with higher propensity for persistence
  - This information can inform warnings on SDSs, recommendations on disposal, and/or decision-making regarding continued pursuit of chemical in R&D

	TBBPA DAE	Cyclemax	HFIPMA
Log K_{ow} (octanol-water)	10.02	3.49	3.02
Boiling Point (°C)	508.66	263.7	93.59
Melting Point (°C)	216.64	29.05	-71.77
Vapor Pressure (mmHg, 25°C)	1.99×10^{-9}	0.0121	49.3
Water Solubility (mg/L)	3.119×10^{-7}	60.17	75.03
Bioconcentration Factor (L/kg wet-weight)	442.4	93.12	45.33

Cardno ChemRisk

What Did We Learn and How Can We Use These Tools?

- With this test run, the tools reasonably predicted the toxicity data available for chemicals
  - Computational tools along with analog identification tools
- Exceptions included when structural alerts originated from moieties with little accessibility
- Need sophisticated interpretation to:
  - Interpret across tools
  - Understand reliability of predictions
  - Account for factors the tool cannot, such as chemical shape
- Nevertheless, the resulting analyses can inform a variety of product stewardship needs
  - Hazard communication
  - Prioritization of lead chemistries
  - Informing regulatory submissions

Leveraging the Framework in Hazard Communication

- Rely on hazard alerts to notify on potential hazards
  - Reliability of prediction will likely dictate either formal classification (Section 2) or use of a hazard statement (Section 11)
- Tailor recommendations on worker protection practices
- Provide recommendations on waste and disposal
- Prioritize types of toxicity testing, if desired, to refine hazard communication

- Example: If a chemical has a prediction for skin sensitization:
  - In Section 11: “Structural and read-across analyses suggest [Chemical X] may cause an allergic skin reaction. Currently, no data are available to confirm this association.”
  - Recommend glove use as standard practice in all forms of hazard communication; other skin protections may be recommended depending on use scenario
  - Consider conducting skin sensitization testing in accordance with appropriate guidance

R&D and Lead Prioritization

- Avoidance of problematic chemistries
  - CMRS
  - PBTs
- Identify needs for targeted toxicity testing
- Comparison of two or more promising chemistries
- Appropriate worker protection during R&D

Cardno ChemRisk

Meeting Regulatory Obligations

- Anticipate regulatory predictions for new chemicals
  - For example, EPA uses many of these tools for predicting hazards under TSCA
  - May inform testing strategy to shorten time to market
- Provide toxicological data to regulatory agencies
  - Improved outcomes in acceptance
  - Potential reduction in burdensome testing
- Respond to regulatory inquiries on chemicals

Conclusions

- Hazard assessment is an important piece of product stewardship from research and development to appearance on the market
- Computational tools are available to bolster hazard assessment of chemicals with little existing data
  - New to company's portfolio
  - In R&D
  - Byproduct or impurity in manufacturing
- Considering multiple lines of evidence and integrating information can be a useful way to anticipate potential hazards associated with such chemicals
- Tools are available to support this kind of activity, even in the absence of conducting empirical testing
- Can offer peace of mind, ensure worker safety, and protect company bottom line by avoiding costly reformulation, regulatory restriction, or litigation down the line

Thank you

Questions?

For more information:
Marisa Kreider, Ph.D., DABT
412-694-7055
Marisa.Kreider@cardno.com