Redefining possible®

Predicting acute toxicity hazard in the absence of experimental data: Case studies from the alternatives assessment paradigm

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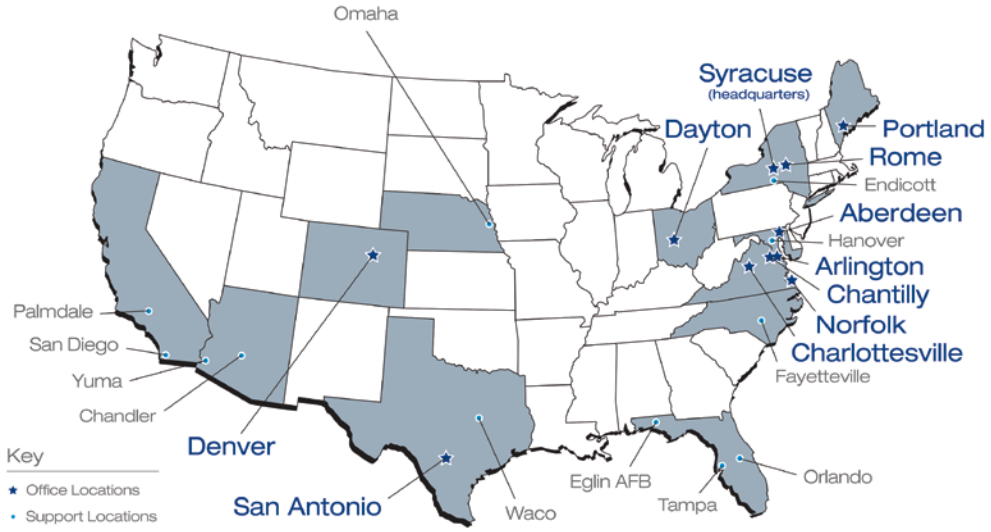
SRC Defense › Environment › Intelligence

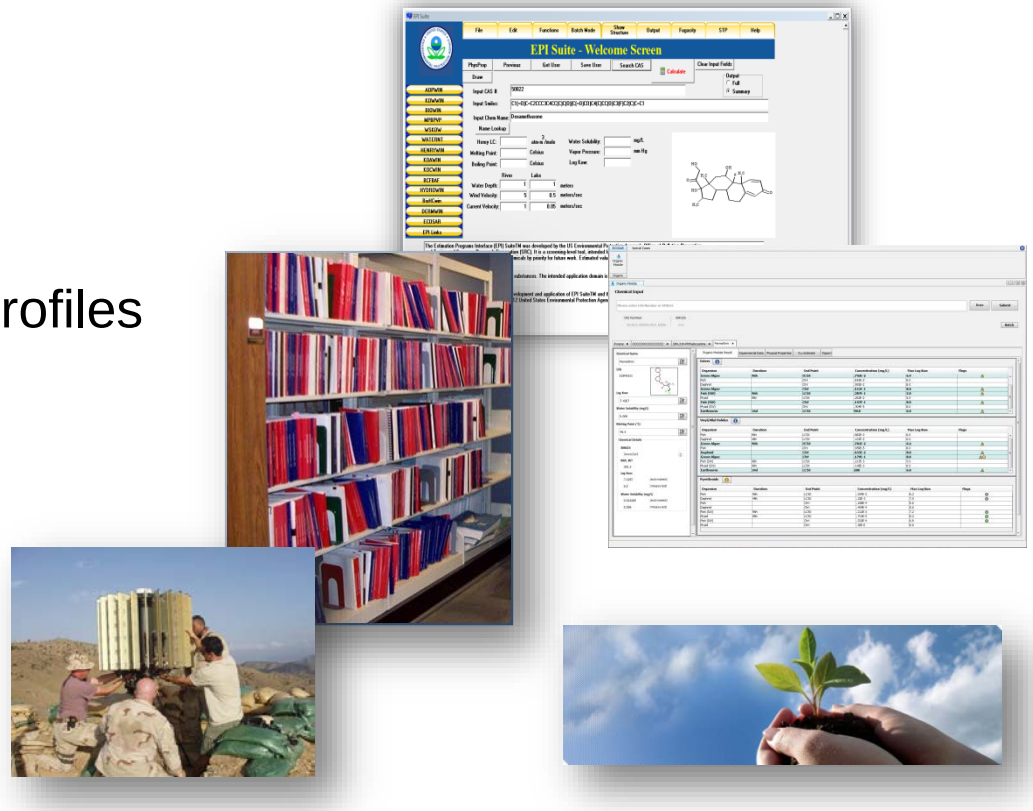
Who Are These Guys?

- Founded in 1957 as Syracuse University Research Corporation as a not-for-profit organization by the NY State Board of Regents
- Became Syracuse Research Corporation in 1976, and SRC, Inc. in 2009

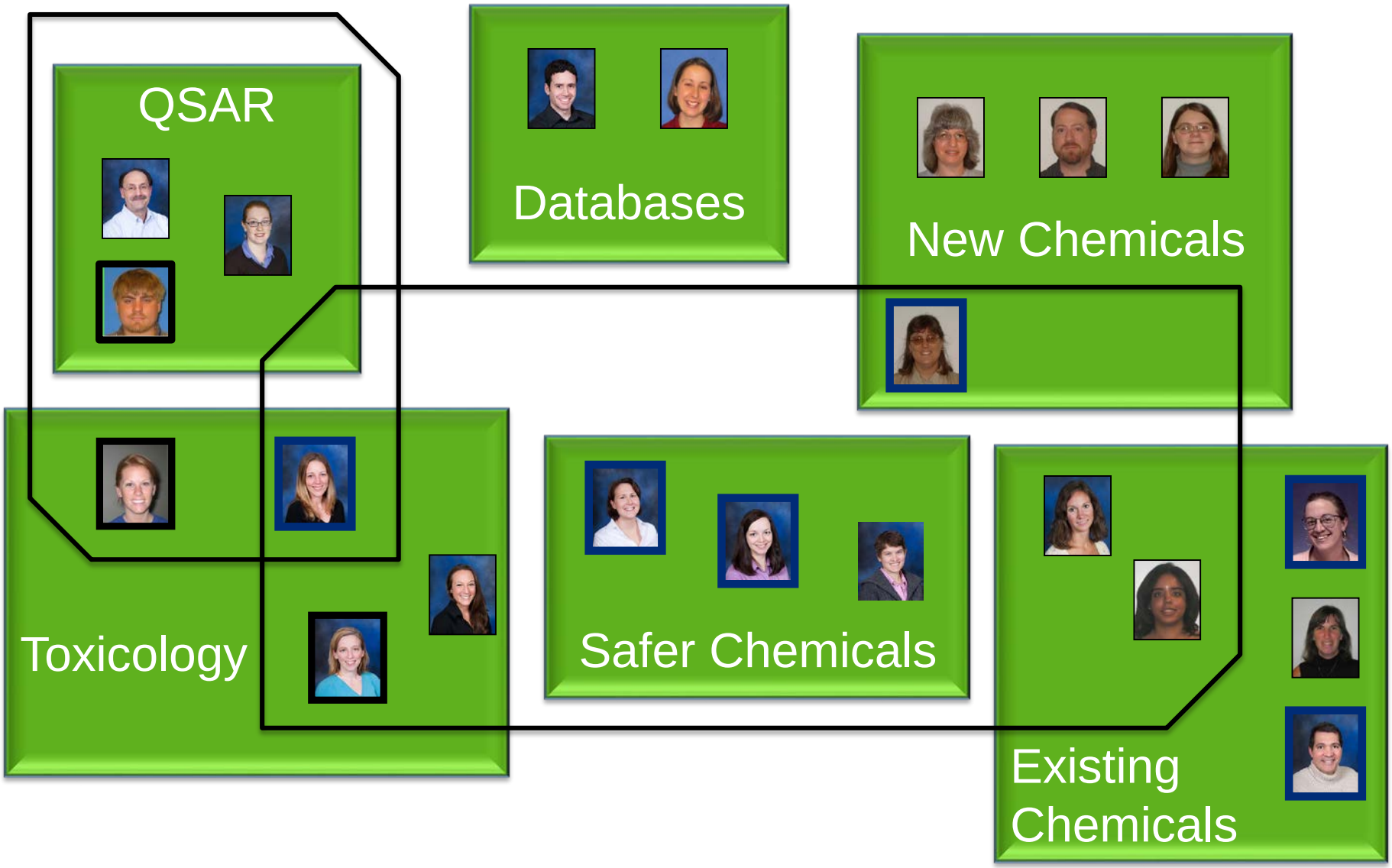


Environmental Health Analysis Group

- EPA
  - New Chemicals program (>25,000 PMNs assessed)
  - Safer Choice/DfE (supported AAs, SPLP, and SCIL since their inception)
  - IRIS
- Other Government
  - NLM/NIH – HSDB
  - CDC/ATSDR Toxicological profiles
  - OSHA – PELs
  - State Agencies
  - DoD



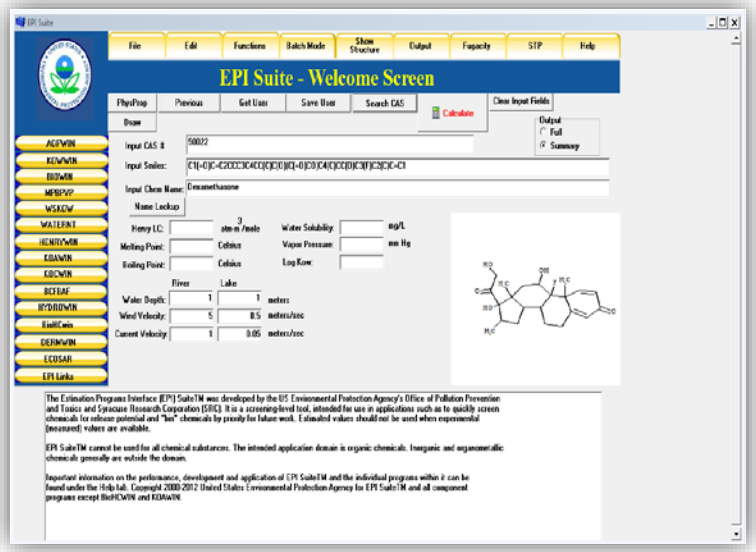
The Chemical Hazard Assessment Group



Disclaimer

- All chemical information presented herein is available in the public domain

- Views expressed are those of the author alone



PBT Characteristics

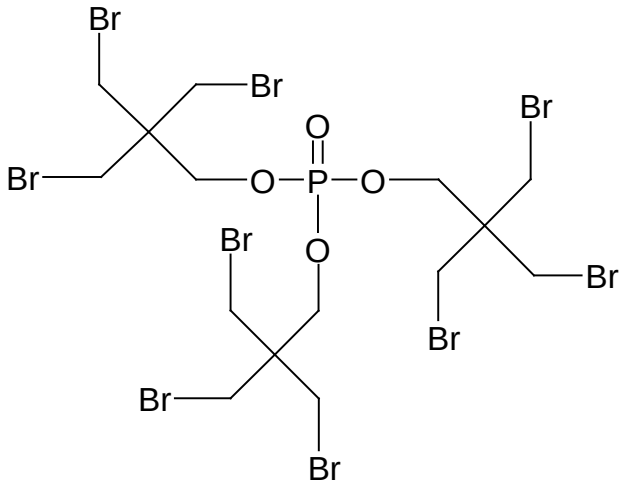
Persistence				QSAR?
	Low	Moderate	High	
Half-life	<60 days	60-180 days	>180 days	✓

Bioaccumulation				
	Low	Moderate	High	
BCF	>1,000	1,000-5,000	>5,000	✓

Aquatic Toxicity				
	Low	Moderate	High	
Acute	>100 mg/L	1-100 mg/L	<1 mg/L	✓
Chronic	>10 mg/L	0.1-10 mg/L	<0.1 mg/L	✓

Hierarchy for Predicting HH Hazard

- Analog
  - Data available on closely related compounds
- Read Across
  - Data available for multiple analogs
- Chemical class
  - Local effects
  - Functional groups
  - Mechanistic basis
- Also considered...
  - Metabolites
  - Reaction products (e.g., hydrolysis)



Predicting Concern, Includes LOW Toxicity

Company	Chemical*	% in Formulation[3]	Human Health Effects							Ecotoxicity		Environmental	
			Cancer Hazard	Skin Sensitizer	Reproductive	Developmental	Neurological	Systemic	Genotoxicity	Acute	Chronic	Persistence	Bioaccumulation
Albemarle	ANTIBLAZE 180 and ANTIBLAZE 195												
	Tris(1,3-dichloro-2-propyl)Phosphate CAS # 13674-87-8	95%	M	L	M	M	L	M	M	M	M	M	L
Albemarle	ANTIBLAZE 182 and ANTIBLAZE 205												
	Proprietary A Chloroalkyl phosphate (1)		M	L	M	M	L	M	M	M	M	M	L
	Proprietary B Aryl phosphate		L	L	M*	M*	M	M*	L	H	H	L	M
	Triphenyl Phosphate CAS # 115-86-6		L	L	L	L	L	M	L	H	H	L	L
Albemarle	ANTIBLAZE V500												
	Proprietary C Chloroalkyl phosphate (2)		M	M	M*	M*	L	M	L	M	M	M	L
	Proprietary B Aryl phosphate		L	L	M*	M*	M	M*	L	H	H	L	M
	Triphenyl Phosphate CAS # 115-86-6		L	L	L	L	L	M	L	H	H	L	L

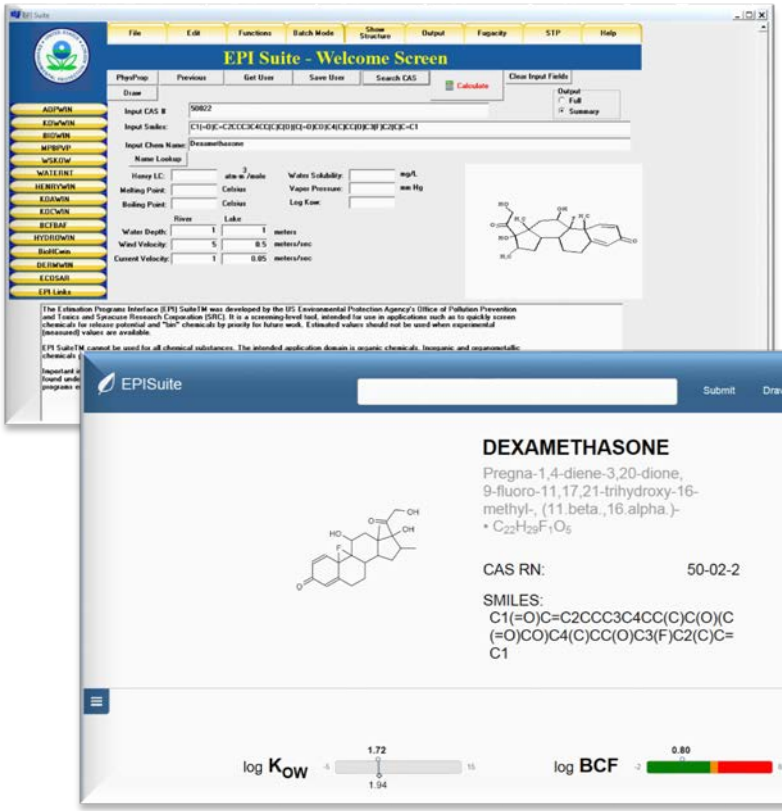
SAFER CHOICE
Meets U.S. EPA Safer Product Standards
epa.gov/saferchoice

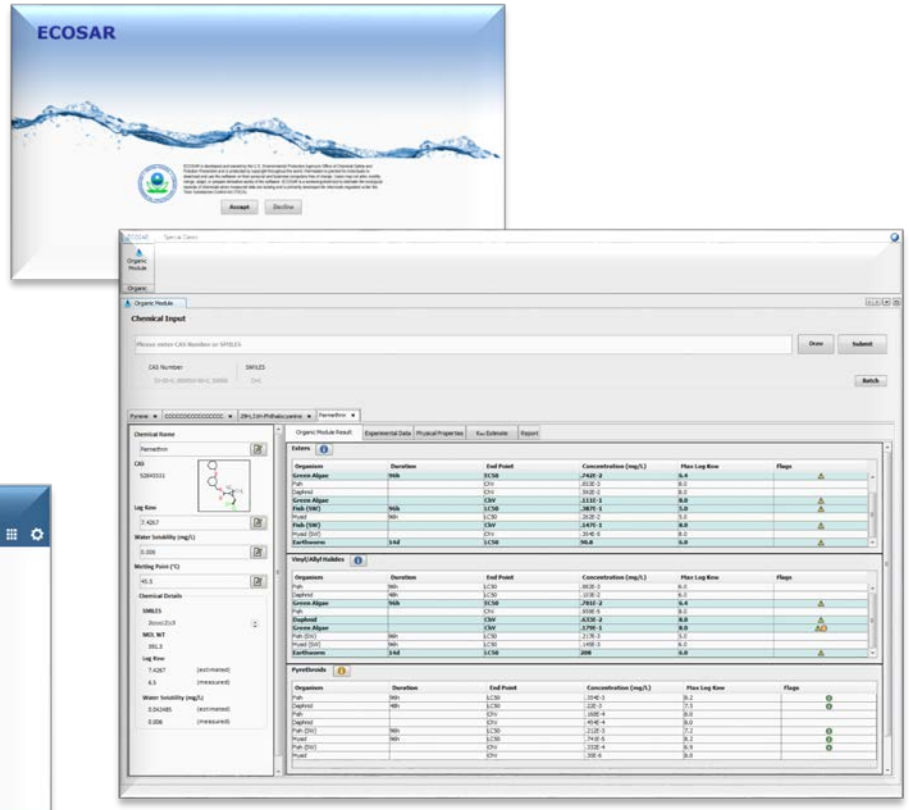
DfE Acute Criteria

Route	VH	H	M	L (P/F)
Oral, LD_{50} (mg/kg bw)	≤50	>50-300	>300-2,000	**>2,000**
Dermal, LD_{50} (mg/kg bw)	≤200	>200-1,000	>1,000-2,000	**>2,000**
Inhalation, LC_{50} (vapor/gas; mg/L)	≤2	>2-10	>10-20	**>20**
Inhalation, LC_{50} (dust/mist/fumes; mg/L/d)	≤0.5	>0.5-1	>1.0-5	**>5**

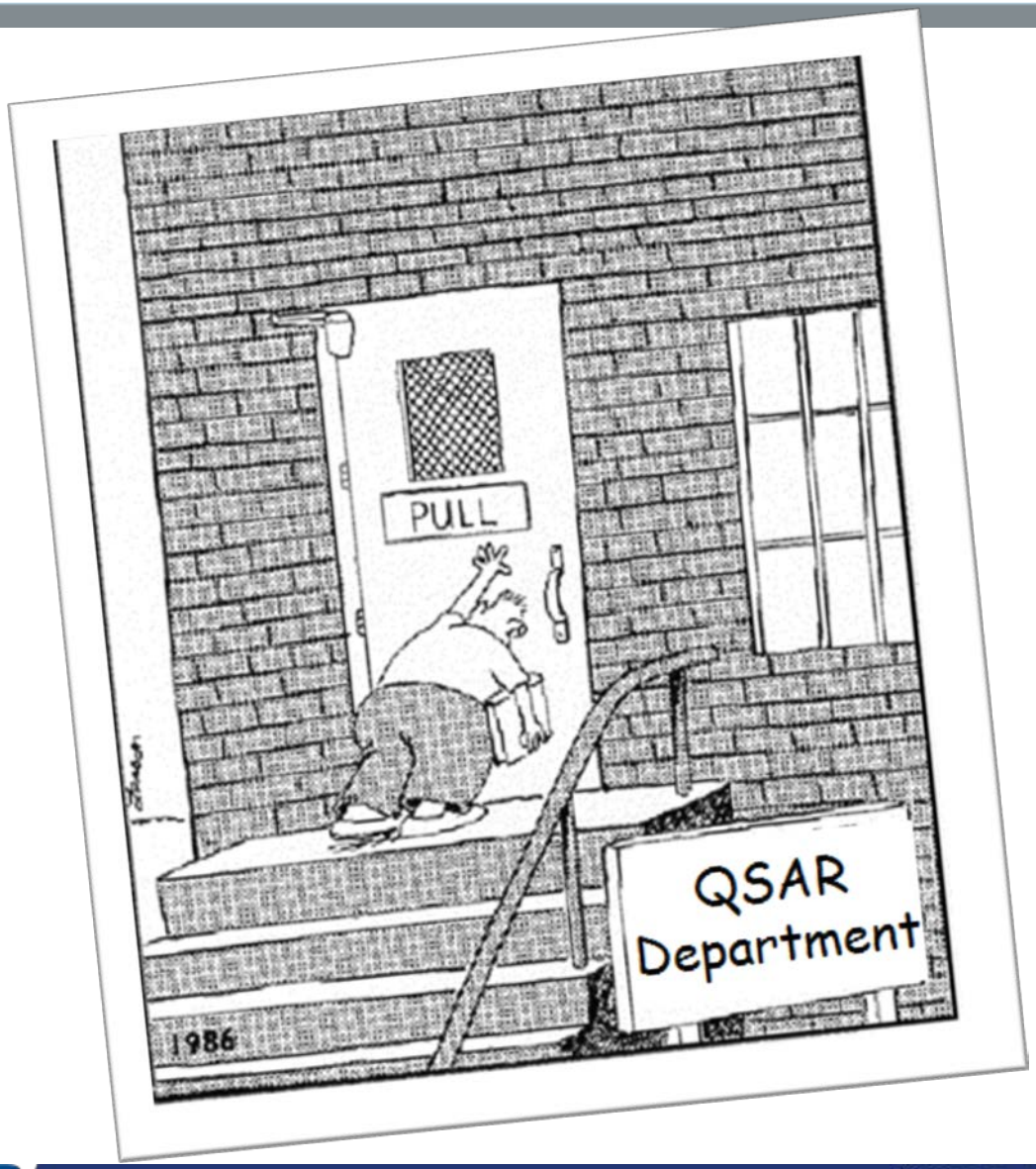
We Are Modelers

EPISuite™





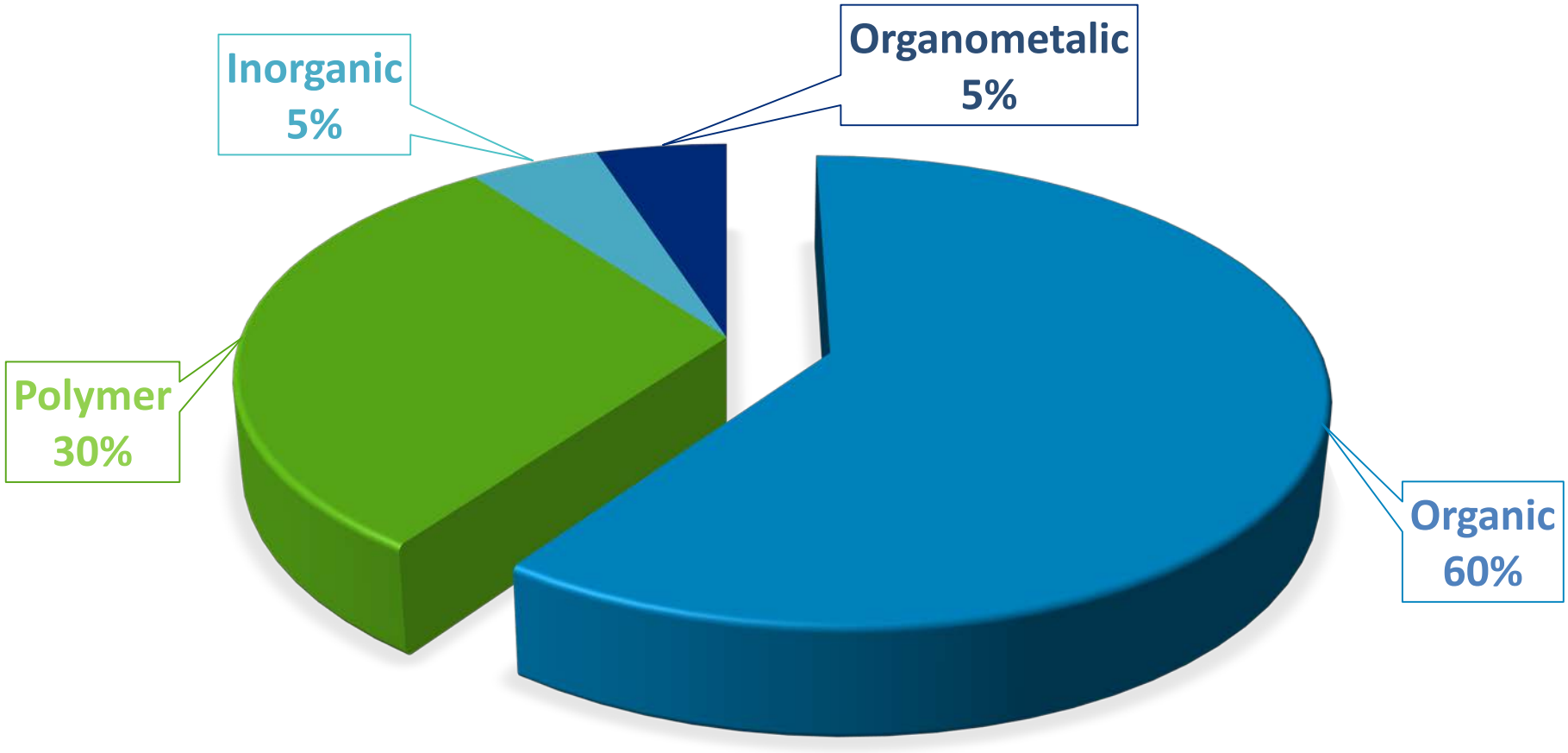
On the Way to Work….



International QSAR Workshop

QSAR 2016 ~ June 13th-17th ~ Miami Beach

What About the Dis-Organics?

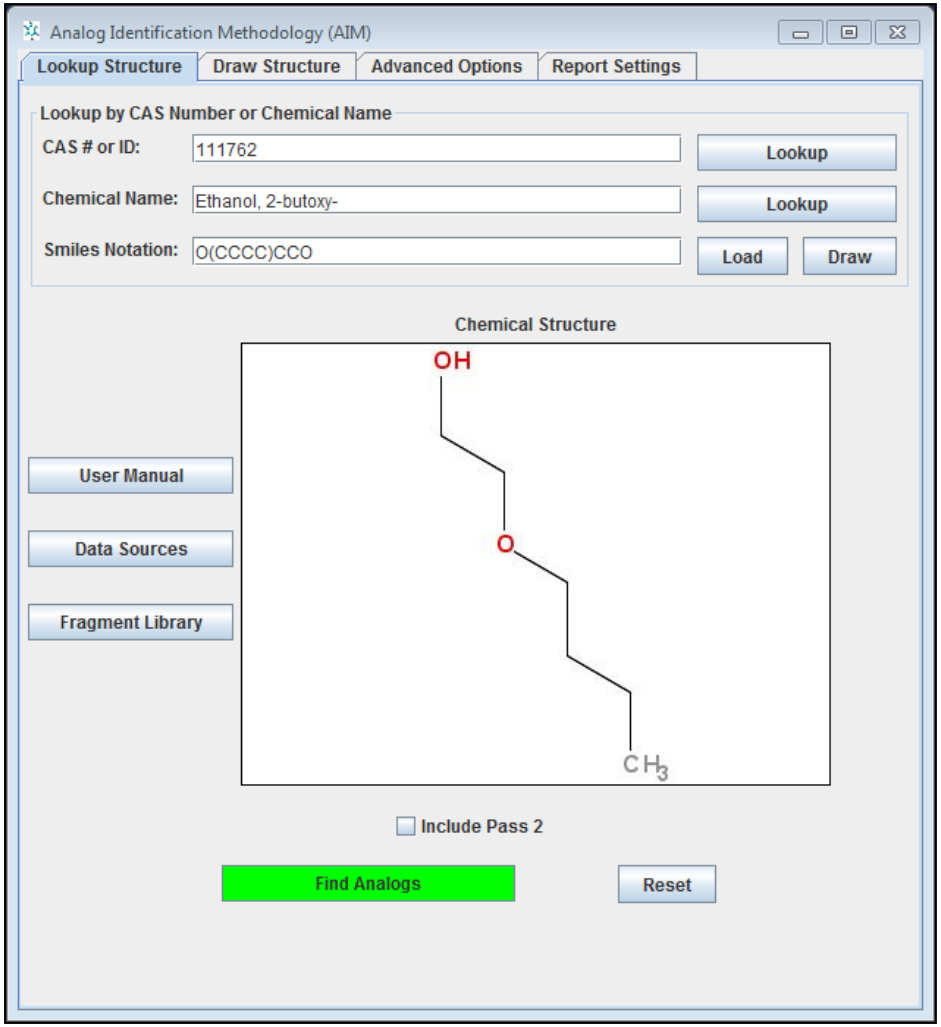


Perhaps from a Chemist's Perspective

- Don't forget the importance of Physical/Chemical properties!

- Mechanistic understanding & verification of:
  - Functional group(s)
  - Mechanism
  - Metabolites
  - Electronic affects
  - Steric demands
  - Initiating event (AOP)
  - Mixtures

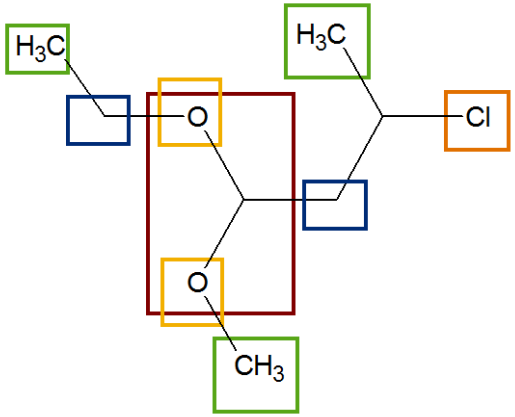
Analog Identification Methodology (AIM)



Product developed to address stakeholder comments from EPA's Sustainable Futures Initiative

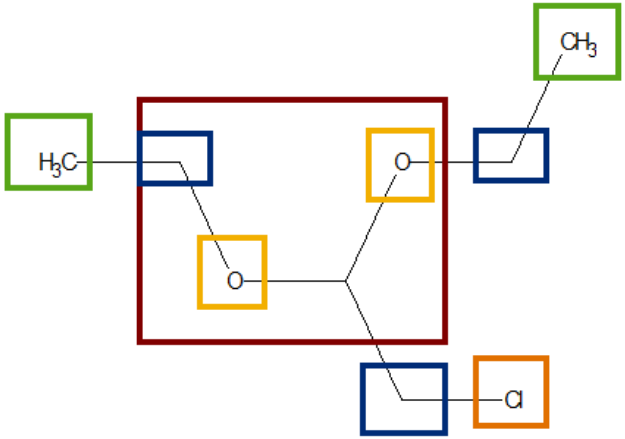
Free download from:
www.epa.gov/oppt/sf/tools/aim.htm

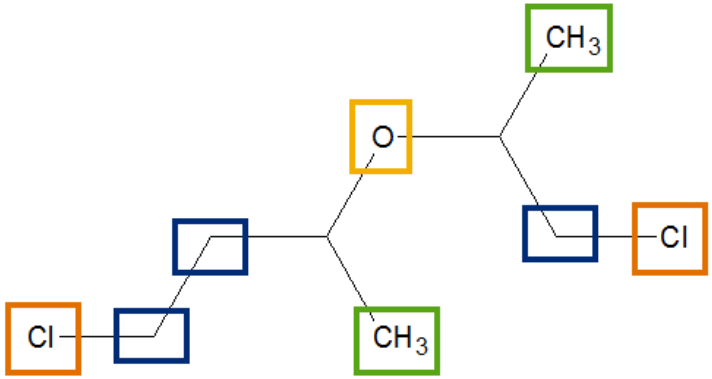
AIM Methodology



Pass 1

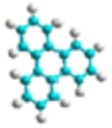
Pass 2



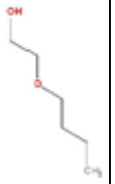


AIM Results

Analog Report
For

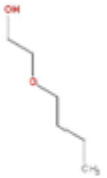


CAS / ID: 111762
Name: Ethanol, 2-butoxy-
SMILE: O(CCCC)CCO
Options: None
Date: Jul 24, 2015 4:22 PM
78 AIM Results Found



Exact Chemical Match

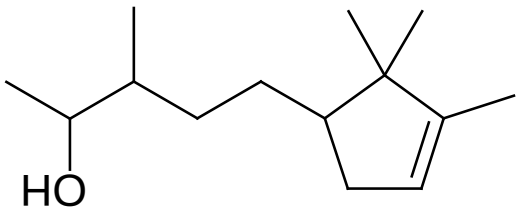
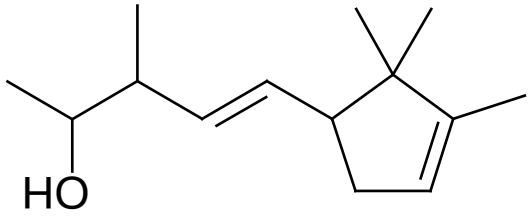
2-BUTOXYETHANOL [111-76-2]
O(CCCC)CCO

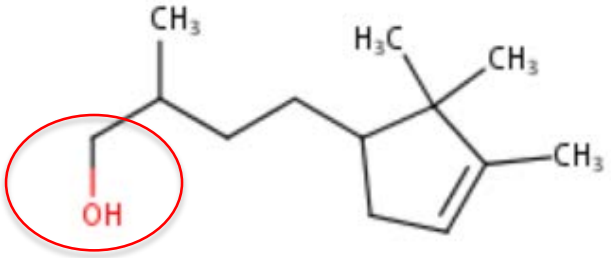


Toxicity Data Available for this Compound

- RTECS
- HPV Challenge
  - OECD HPV
    ** May also be located at: OECD*
- ECOTOX
- TSCATS II
- ACToR
- TSCATS
- IRIS

AIM Example

Name	Sandalore	Ebanol
Structure		
CAS No.	65113-99-7	67801-20-1
Acute toxicity	Pass	Pass

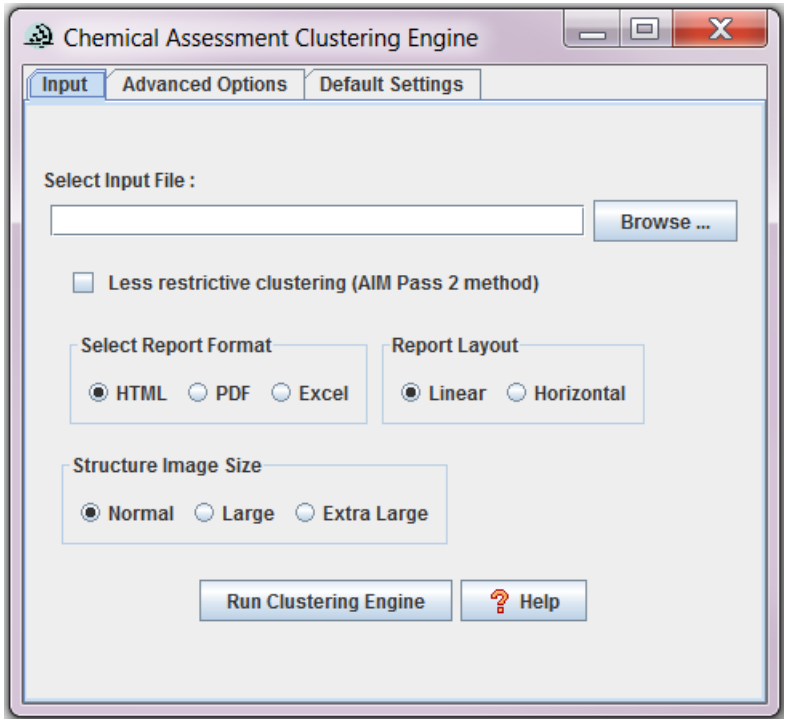


Similarity = 91%

Clustering - ChemACE

ChemACE

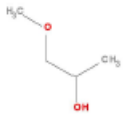
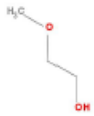
- **Chem**ical **A**ssessment **C**lustering **E**ngine
- Useful tool for building potential fragrance clusters
- Designed for non-experts
- Clusters chemicals from a user-supplied list based on common fragments
- Methodology defines clusters where members are analogs of each other



Free download at:
www.epa.gov/oppt/sf/tools/chemace.htm

Clustering (ChemACE)

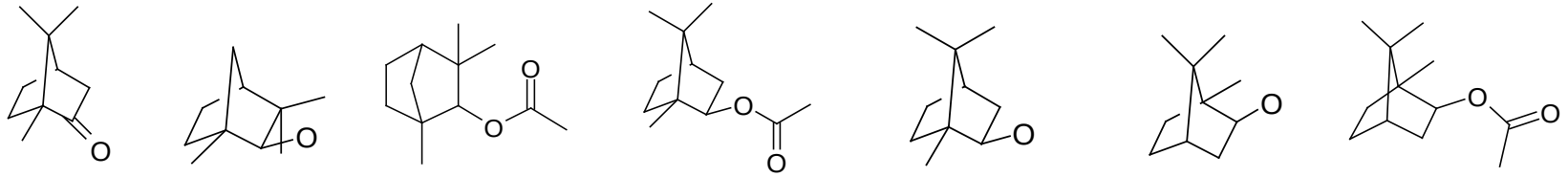
Cluster: 5

						
ID	107982	109864	110805	111762	111900	112345
SMILES	O(CC(O)C)C	O(CCO)C	O(CCO)CC	O(CCCC)CCO	O(CCOCC)CCO	O(CCOCCO)CCCC
Name	1-Methoxy-2-Propanol	2-Methoxyethanol	2-Ethoxyethanol	2-Butoxyethanol	Diethylene Glycol Monoethyl Ether	Diethylene Glycc Monobutyl Ether
Best MOA	None	None	None	MOA Evaluation	None	None

Case Studies

Organics

Read Across – Norobornyl Fragrances



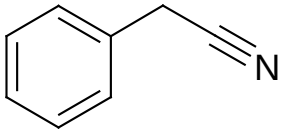
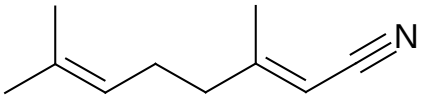
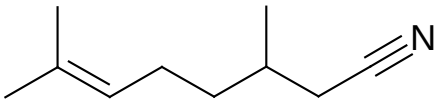
P; B; T	VL; L; M	L; M; M	L; M; H	VL; M; VH	L; M; H	L; L; M	L; M; H
Acute	Fail	Fail (Analog)	Fail (Analog)	Fail (Analog)	Fail (Analog)	Fail (Analog)	Fail (Analog)

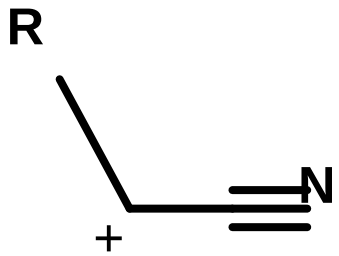
Rat (inhalation), LD_{50} = 0.5 mg/L (ECHA)

Rat (inhalation-dust), 2-hr, LD_{50} >10 mg/L (ECHA)

Mouse (inhalation), 3-hr, LD_{Lo} = 0.4 mg/L (ChemID)

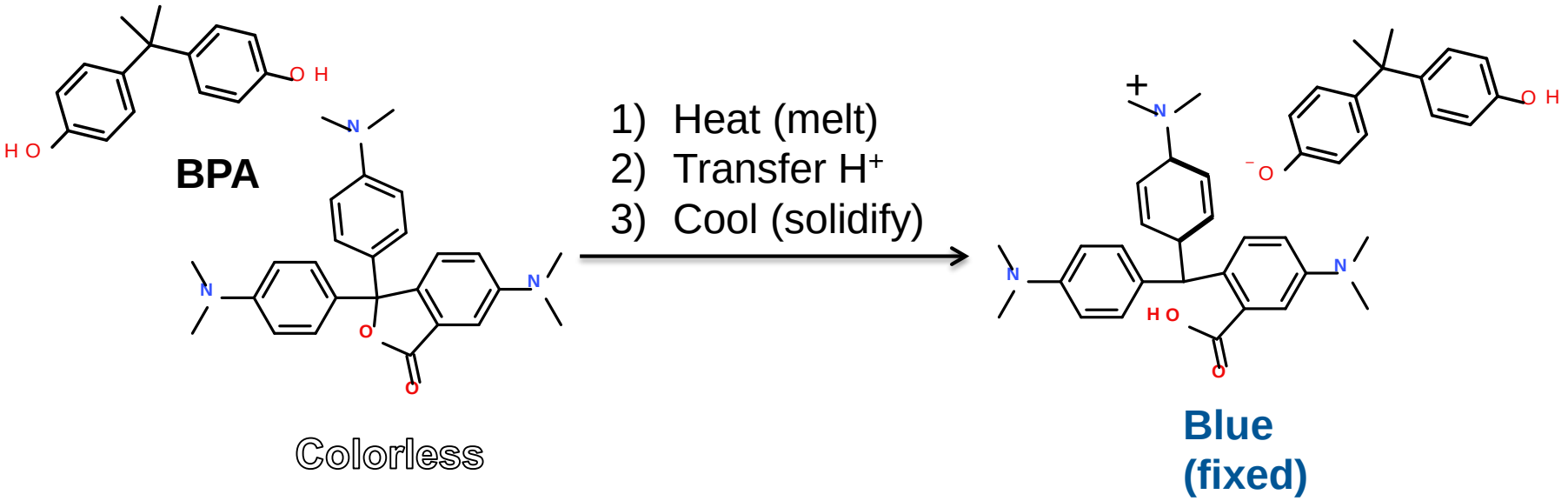
Cyanide Formation from Nitriles

Name	Benzyl cyanide	Geranyl nitrile	Citronellyl nitrile
Structure			
Rat Acute LD_{50} (mg/kg)	270	3,100	5,300
Rabbit Acute LD_{50} (mg/kg)	270	4,300	No data



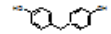
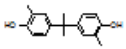
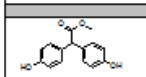
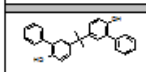
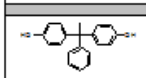
Structural alert for nitriles when stabilized

BPA In Thermal Paper

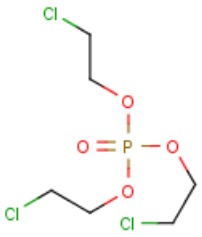
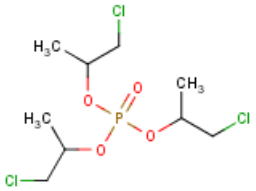
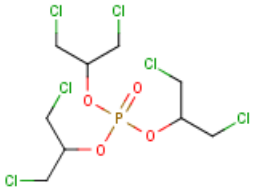


Limited Data – Read Across from BPA

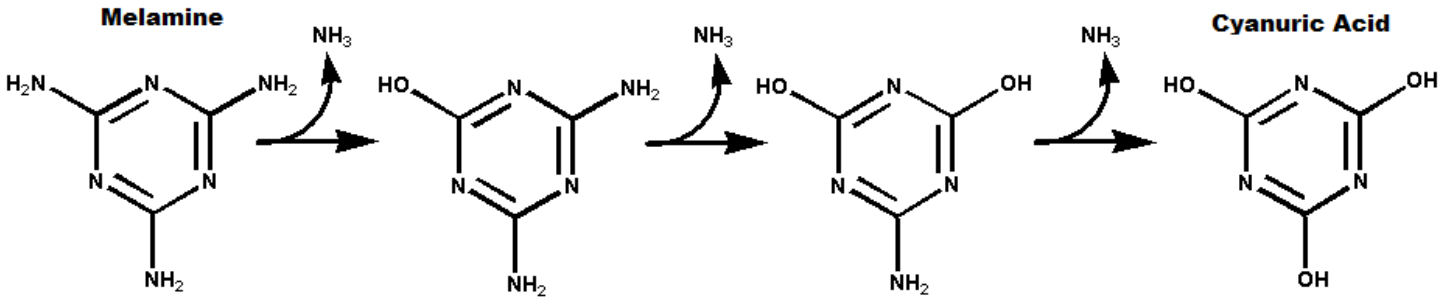
VL = Very Low hazard L = Low hazard M = Moderate hazard H = High hazard VH = Very High hazard — Endpoints in colored text (VL, L, M, H, and VH) were assigned based on empirical data. Endpoints in black italics *(VL, L, M, H,* and *VH)* were assigned using values from estimation software and professional judgment.
§ Based on analogy to experimental data for a structurally similar compound.

Structure	Chemical (for TSCA inventory name and relevant trade names see the individual profiles in Section 4.8)	CASRN	Human Health Effects										Aquatic Toxicity		Environmental Fate	
			Acute Toxicity	Carcinogenicity	Genotoxicity	Reproductive	Developmental	Neurological	Repeated Dose	Skin Sensitization	Respiratory Sensitization	Eye Irritation	Dermal Irritation	Acute	Chronic	Persistence	Bioaccumulation
	Bisphenol A 2,2-bis(p-hydroxyphenyl)propane	80-05-7	L	M	L	M	H	*M*	M	M		M	M	H	H	VL	L
	Bisphenol F Bis(4-hydroxyphenyl)methane	620-92-8	L	*M*	L	*M* §	*H* §	*M*	H	L		VH	*M* §	M	*H*	L	L
	Bisphenol C 2,2'-Bis(4-hydroxy-3-methylphenyl)propane	79-97-0	*L* §	*M*	M	*M* §	*H* §	*M*	*M* §	*M* §		*H* §	*M* §	H	*H*	M	*M*
	MBHA Methyl bis(4-hydroxyphenyl)acetate	5129-00-0	*L* §	*M*	*L* §	*M* §	*H* §	*M*	*M* §	L		*M* §	*M* §	*H*	*H*	*M*	*L*
	BisOPP-A 4,4'-Isopropyllidenebis(2-phenylphenol)	24038-68-4	*L* §	*M*	*L* §	*M* §	*H* §	*M*	*M* §	*M* §		*M* §	*M* §	*L*	*H*	*H*	*M*
	Bisphenol AP 4,4'-(1-Phenylethylidene)bisphenol	1571-75-1	*L* §	*M*	*L* §	*M* §	*H* §	*M*	*M* §	*M* §		*M* §	*M* §	*H*	*H*	*H*	*M*
	Substituted phenolic compound, PROPRIETARY #1		*L* §	*M*	L	*M* §	*H* §	*M*	*M* §	*M* §		*M* §	*M* §	*H*	*M*	*M*	*L*
	Substituted phenolic compound, PROPRIETARY #2		*L* §	*M*	*L* §	*M* §	*H* §	*M*	*M* §	*M* §		*M* §	*M* §	*H*	*H*	*H*	*H*

Flame Retardant Alternatives

			
CASRN	115-96-8	13674-84-5	13674-87-8
Chemical	Tris (2-chloroethyl) phosphate	Tris (2-chloro-1-methylethyl) phosphate	Tris(1,3-dichloro-2-propyl)phosphate
Molecular Weight	285.49	327.57	430.91
State	Liquid	Liquid	Liquid
Acute	**46.4** mg/kg Rat	**930** mg/kg Rat	**>2000** mg/kg Rat

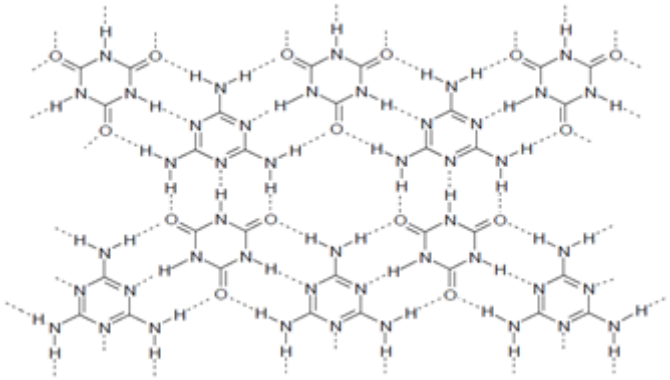
Melamine (TBBPA AA)



Rat LD_{50} >3,160 mg/kg

Rat LD_{50} >5,000 mg/kg

Super-strong hydrogen Bonds (pH dependent)

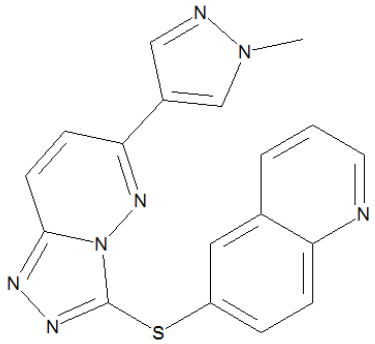


Forms insoluble crystals in kidneys

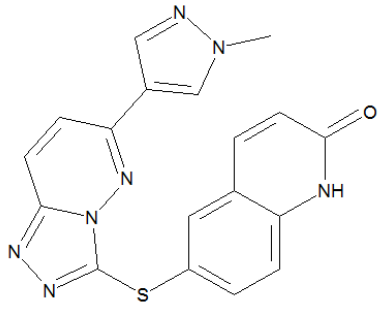
Can QSARs be expected to provide reasonable results for these exceptions?

Don’t forget the properties!!!

Phase I clinical testing, all subjects experienced acute renal failure (Mike Bolger Webinar)



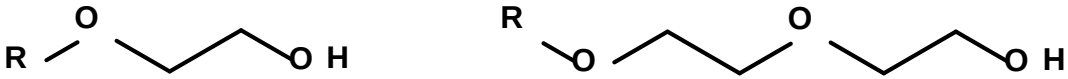
Parent: Soluble

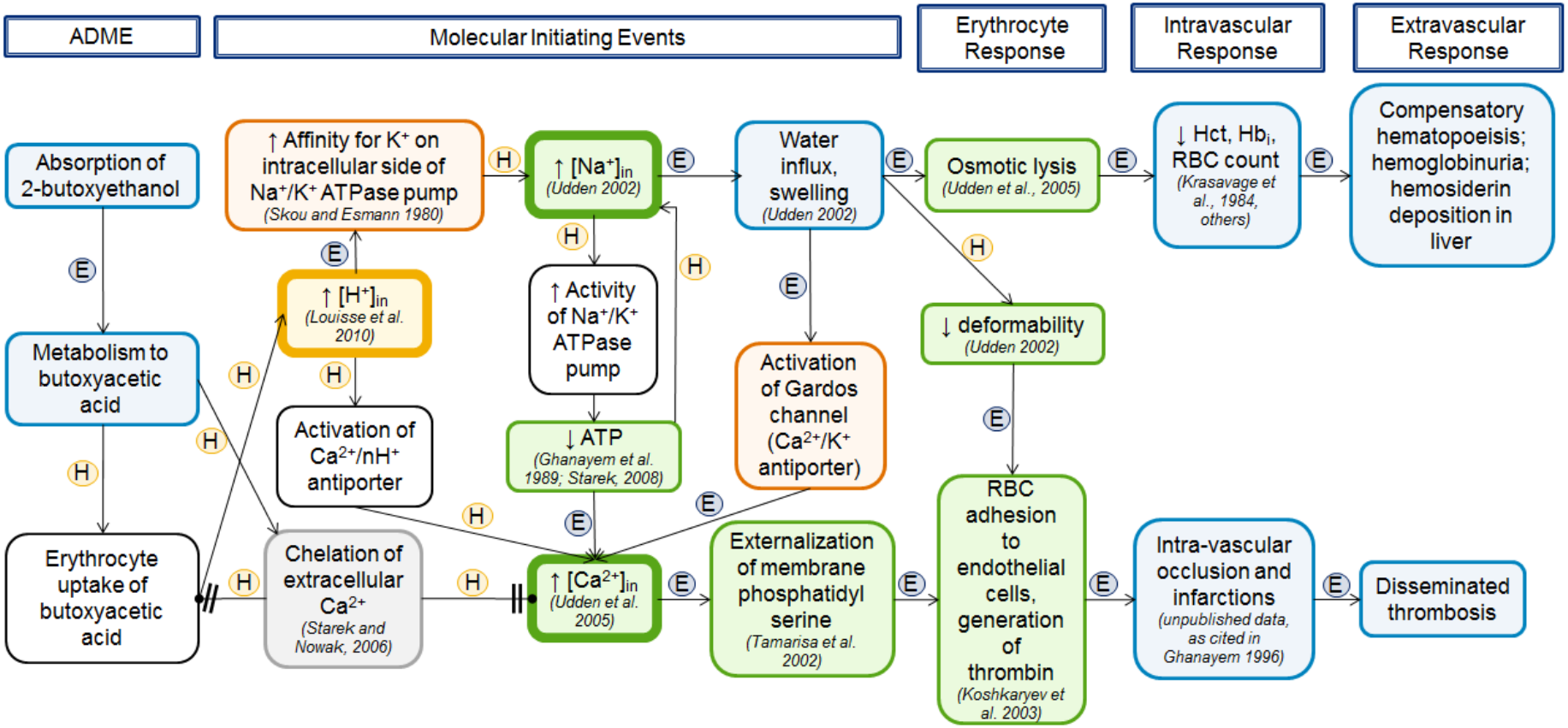


Metabolite: Not Soluble

“…physicochemical properties can serve a critical role in alternatives assessment processes…” (NAS 2014; *Tickner, et al. 2015*)

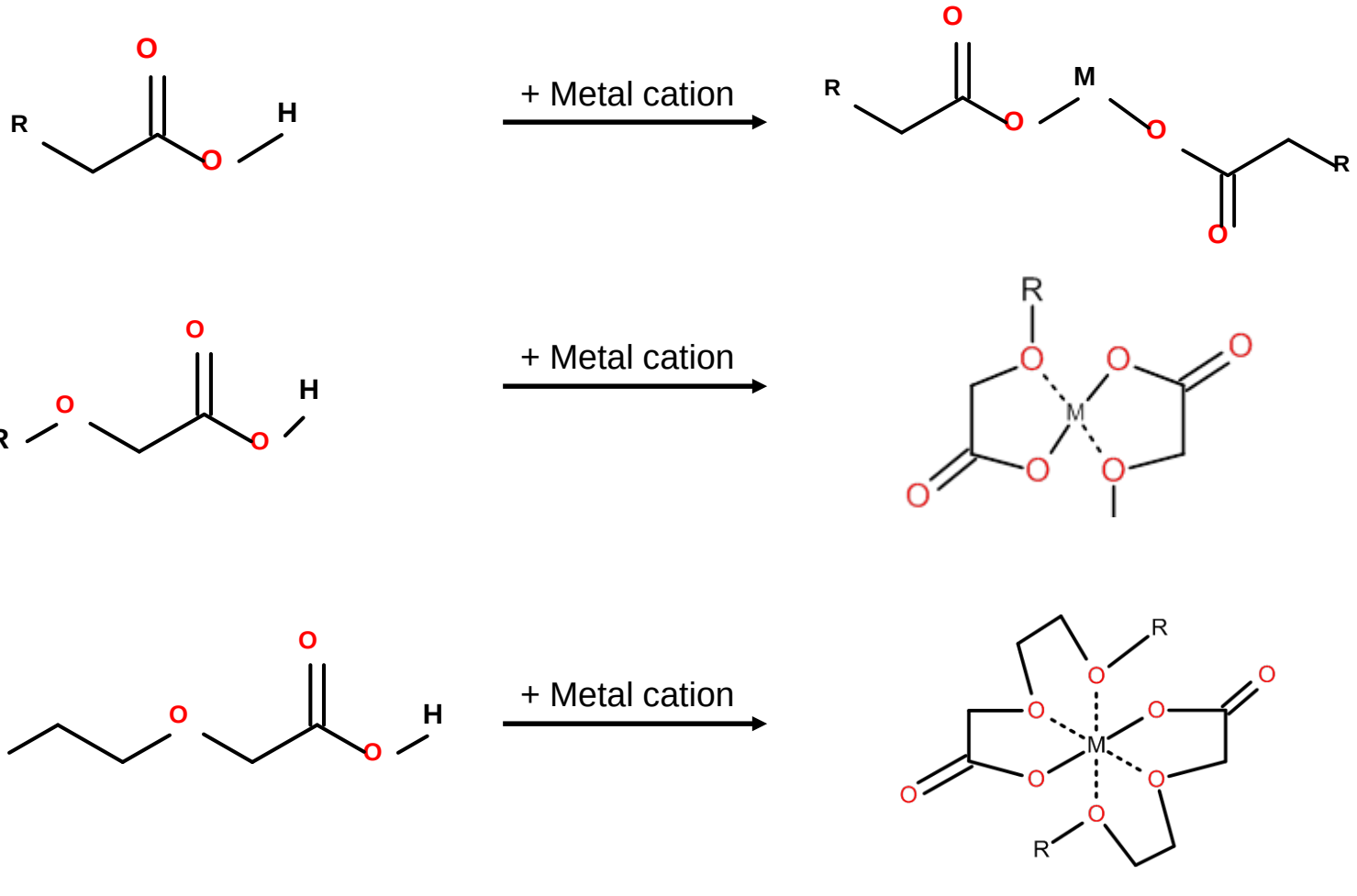
AOP Development





Bold outline: potential molecular initiating event

AOP - Oxygen is Important



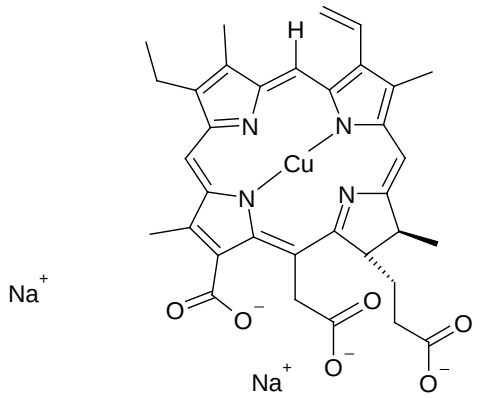
Case Studies

Inorganics, Organometallics and Polymers

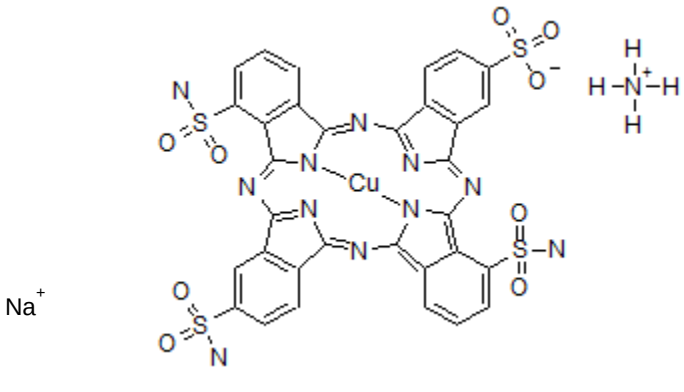
Inorganics and Organometallics

Chemicals	LD_{50}	Safer Choice (DfE)
• Dicopper chloride trihydroxide • Copper sulfate pentahydrate • Dicopper oxide	299-2,006 mg/kg; in rat and mice	**Fail**

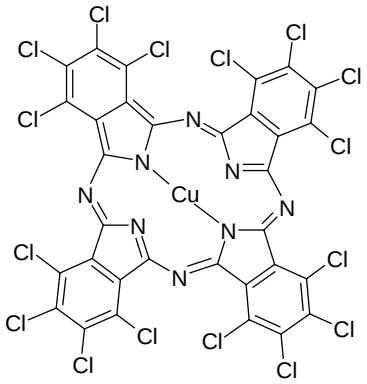
Porphyrins (includes phthalocyanines) – 6 members total, data on 2



Chlorophyll

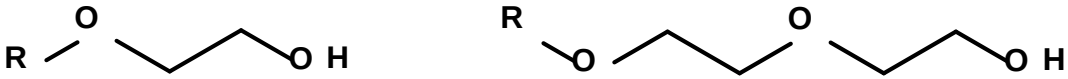


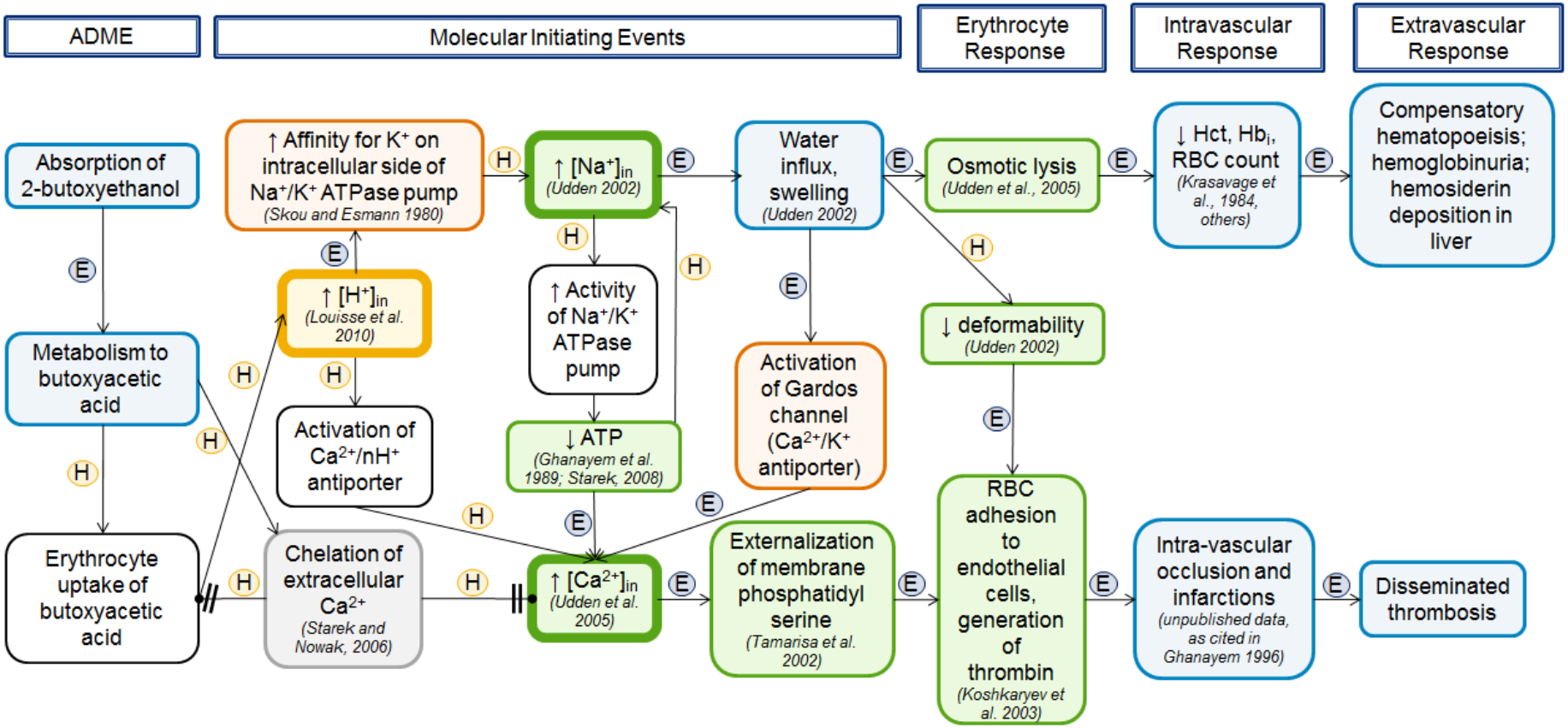
C.I. Pigment Green 7
2,000 mg/kg



Direct Blue 86
>5,000 mg/kg

AOP Development





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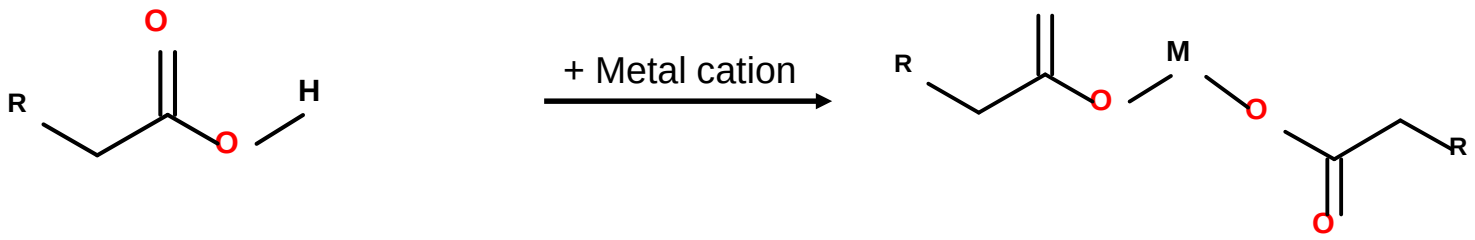
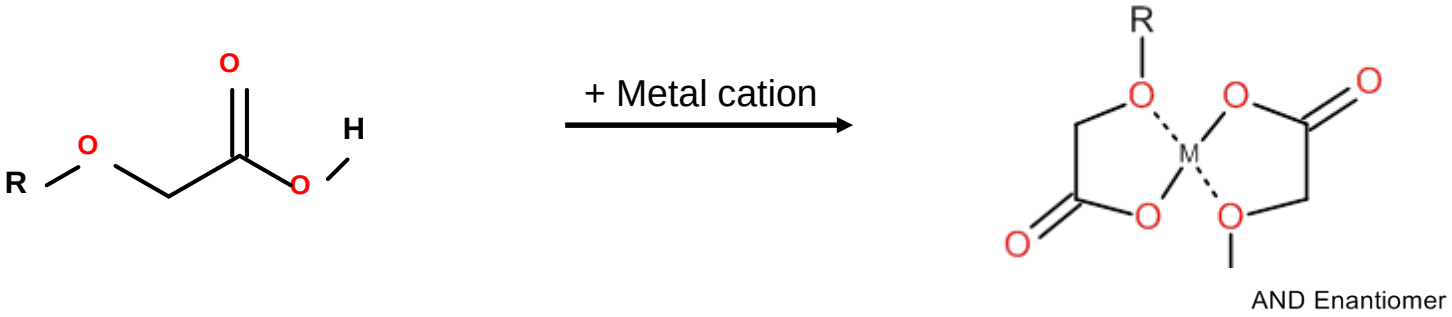
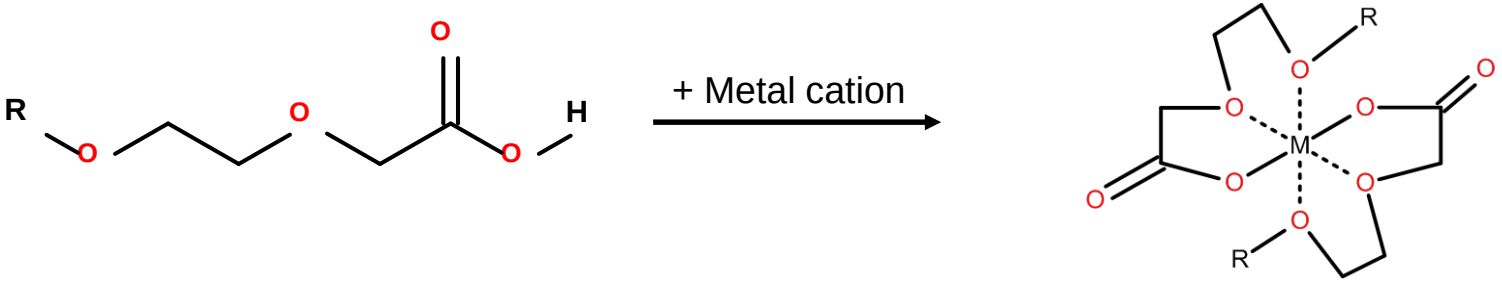
AOP - Oxygen is Important





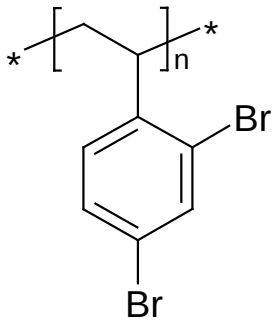


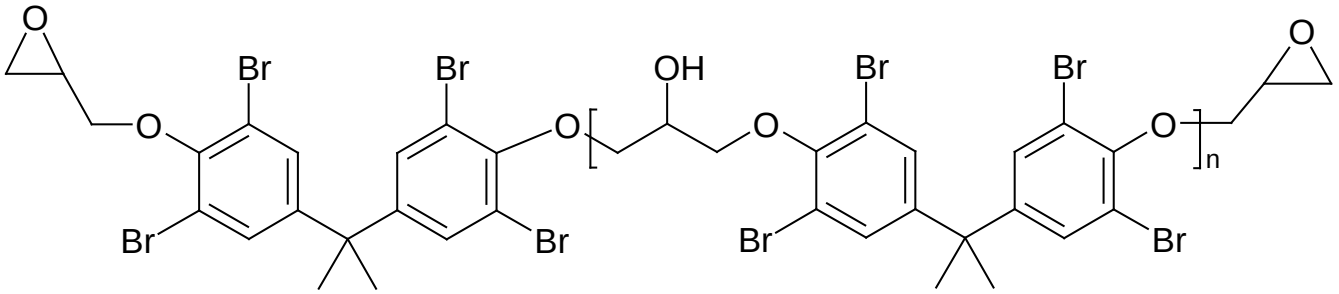
Predicting Polymer Toxicity

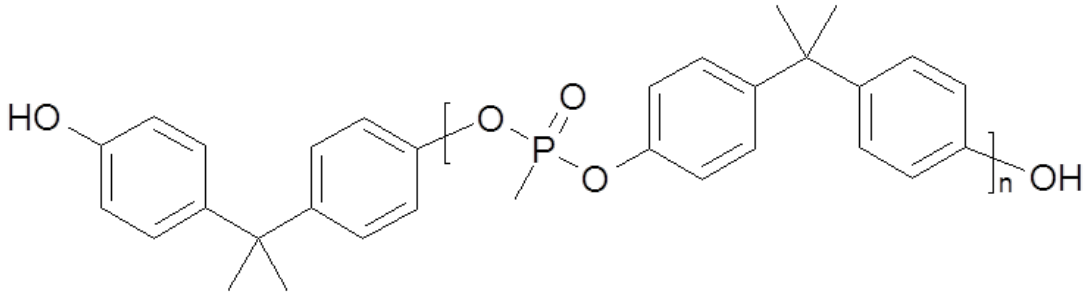
- **Category 1**
  - Low molecular weight polymers
  - MW_n <1,000
- **Category 2**
  - Polymers with high & low MW components
  - MW_n >1,000 and ≥25% with MW <1,000; ≥10% with MW <500
- **Category 3**
  - High molecular weight polymers
  - MW_n >1,000
- Polymers with potential toxicity are:
  - Swellable polymers
  - Pendant functional groups of concern (e.g., epoxides)

http://www.epa.gov/oppt/newchems/pubs/hmwtpoly.htm

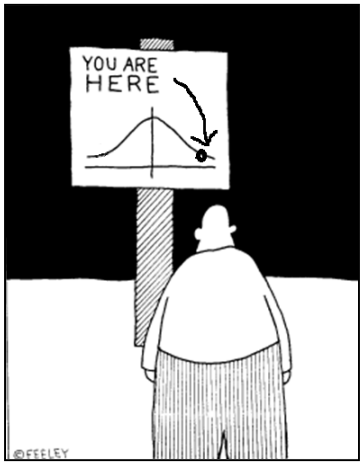
Polymer Flame Retardant Alternatives







Thank You! Questions?



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