CRITICAL EVALUATION OF GREENSCREEN® BENCHMARK 1 CHEMICALS TO IDENTIFY STRUCTURAL ALERTS

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Outline

- Introduction
  - Overview of Benchmark 1 Chemicals
  - Overview of GreenScreen® for Safer Chemicals (GreenScreen)
- Project Summary
  - Overview of Structural Alerts
  - Results
- Future Goals
- Questions?

Overview of Benchmark 1 Chemicals

- Product formulators need tools to quickly identify chemicals of high concern
- GreenScreen classifies the most hazardous chemicals, including PBT (persistent, bioaccumulative and toxic), CMR (carcinogenicity, mutagenicity and reproductive toxicity) or endocrine active chemicals, as Benchmark 1

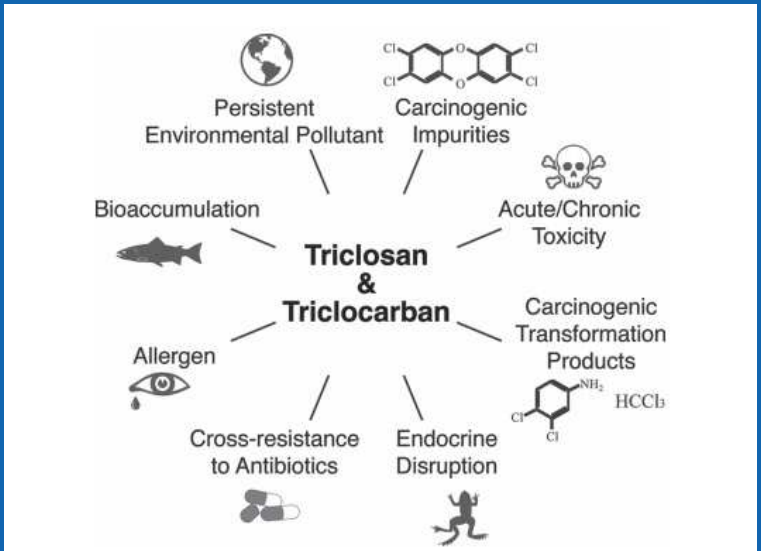


Image by Jason Drees, the Biodesign Institute at Arizona State University, produced for Rolf U. Halden's paper: On the Need and Speed of Regulating Triclosan and Triclocarban in the United States. *Environ. Sci. Technol.* 2014, 48, 3603–3611. Reproduced with permission.

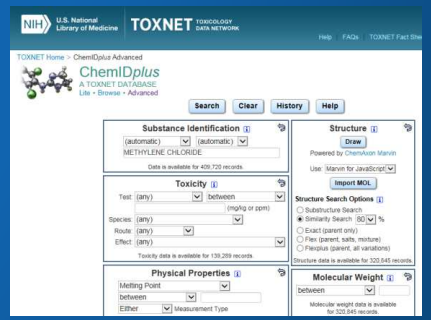
Overview of GreenScreen® for Safer Chemicals

- The GreenScreen is a comparative Chemical Hazard Assessment (CHA) method developed by Clean Production Action
- GreenScreen is freely and publicly accessible, transparent, and peer reviewed
- Builds on the U.S. EPA DfE Alternatives Assessment approach and aligned with national and international precedents (OECD, GHS, REACH)

- All supporting resources at: http://www.greenscreenchemicals.org/

Overview of GreenScreen® for Safer Chemicals, ctd.

- Collect and evaluate data for 18 human health, environmental, and physical endpoints from relevant sources (e.g., test data, literature, models, analogs, hazard lists, etc.) for the chemical under assessment
- Prepared by scientists, toxicologists, and/or CPA licensed profilers.
- Assign level of concern (e.g., vH, H, M, L, or vL) for each of the 18 endpoints
  - Level of confidence for each hazard endpoint (identified by bold or italic font)
- Hazard scores are used to assign an overall Benchmark score, which is a simple way to compare relative hazards of chemicals.



Overview of GreenScreen® for Safer Chemicals, ctd.

Hazard Endpoints Evaluated in GreenScreen

Human Health Group I	Human Health Group II and II*	Environmental Toxicity & Fate	Physical Hazards
Carcinogenicity	Acute Toxicity	Acute Aquatic Toxicity	Reactivity
Mutagenicity & Genotoxicity	Systemic Toxicity & Organ Effects	Chronic Aquatic Toxicity	Flammability
Reproductive Toxicity	Neurotoxicity		
Developmental Toxicity	Skin Sensitization	Persistence	
	Respiratory Sensitization		
Endocrine Activity	Skin Irritation	Bioaccumulation	
	Eye Irritation		

The GreenScreen® assesses hazards for 18 human health, environmental, and physical endpoints

Overview of GreenScreen® for Safer Chemicals, ctd.

GreenScreen® Hazard Criteria Table

	Information Type	Information Source	List Type		High (H)	Moderate (M)	Low (L)	
Carcinogenicity (C)	Data	GHS Criteria & Guidance			GHS Category 1A (Known) or 1B (Presumed) for any route of exposure	GHS Category 2 (Suspected) for any route of exposure or limited or marginal evidence of carcinogenicity in animals (See Guidance)	Adequate data available, and negative studies, no structural alerts, and GHS not classified.	
	A Lists	EPA-C (1986)	Authoritative		Group A, B1 or B2	Group C	Group E	
		EPA-C (1996, 1999, 2005)	Authoritative		Known or Likely		Not Likely	
		EU CMR (1)	Authoritative		Category 1 or 2	Category 3		
		EU CMR (2)	Authoritative		Carc 1A or 1B	Carc 2		
		EU H-statements	Authoritative		H350 or H350i	H351		
		EU R-phrases	Authoritative		R45 or R49	R40		
		EU SVHC	Authoritative		Reason for inclusion: Carcinogenic			
		GHS-[COUNTRY]* Lists (*Korea, Japan, Indonesia, Australia, Europe, New Zealand, and Taiwan)	Screening		Category 1A or 1B	Category 2	Not Classified	
		IARC	Authoritative		Group 1 or 2A	Group 2B	Group 4	
		MAK	Authoritative		Carcinogenic Group 1 or 2	Carcinogenic Group 3, 4, or 5		
		NIOSH-C	Authoritative		Occupational Cancer			
		NTP-RoC	Authoritative		Known or Reasonably Anticipated			
		Prop 65	Authoritative		Known to the state to cause cancer			
	B Lists	EPA-C(1986)	Authoritative		Group D			
		EPA-C (1999)	Authoritative		Suggestive Evidence, but not sufficient to assess human carcinogenic potential			
		EPA-C (2005)	Authoritative		Suggestive evidence of carcinogenic potential			
		IARC	Authoritative		Group 3			

Overview of GreenScreen® for Safer Chemicals, ctd.

Example of Completed Hazard Summary Table

Group I Human					Group II and II* Human								Ecotox		Fate		Physical	
Carcinogenicity	Mutagenicity/Genotoxicity	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
H	**H**	**H**	**H**	*M*	**L**	**vH**	**H**	**M**	**H**	**L**	*L*	**H**	**H**	**H**	**H**	**vL**	**vL**	*L*	**H**

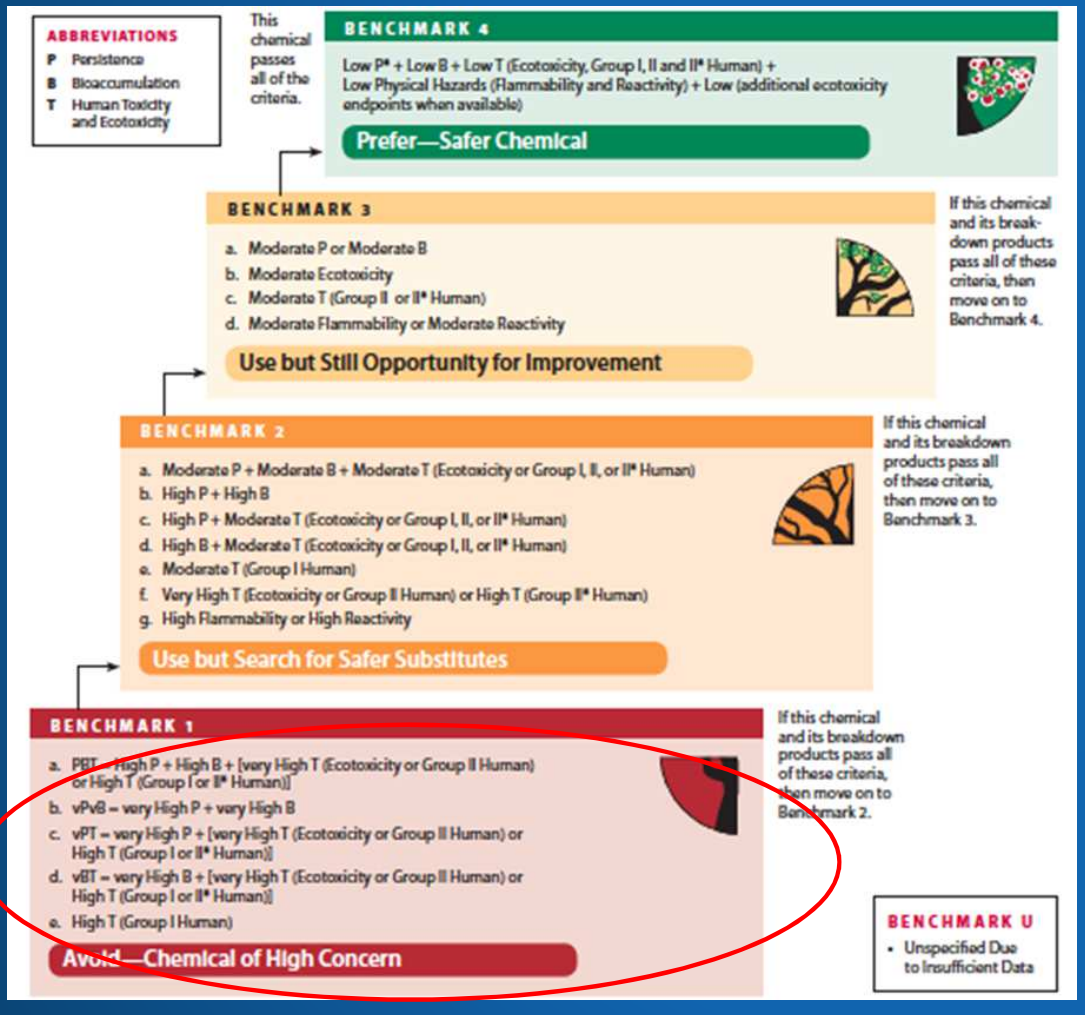
Level of Confidence

Bold vH, H, M, L, or vL = measured data or high quality surrogate

DG= data gap

Italic vH, H, M, L, or vL = estimated data (analog or model)

Overview of GreenScreen® for Safer Chemicals, ctd.



- The combination of hazard classifications for 18 assessed endpoints (Step 1) translates into a Benchmark score ranging from 1-4

- A Benchmark score supports decision-making:
  - BM1 – phase out
  - BM2 – manage to use safely
  - BM3 – getting there
  - BM4 – inherently low hazard

Benchmark U = Undetermined due to insufficient data

← **Aligned with Regulatory Drivers**

Benchmarking Example – Benzene

Group I Human					Group II and II* Human							Ecotox		Fate		Physical	
Carcinogenicity	Mutagenicity/Genotoxicity	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
H	H	H	H	M	L	vH	H	M	H	L	L	H	H	vL	vL	L	H

GS BENCHMARK 1

a. PBT = High P + High B + [very High T (Ecotoxicity or Group II Human) or High T (Group I or II* Human)]

b. vPvB = very High P + very High B

c. vPT = very High P + [very High T (Ecotoxicity or Group II Human) or High T (Group I or II* Human)]

d. vBT = very High B + [very High T (Ecotoxicity or Group II Human) or High T (Group I or II* Human)]

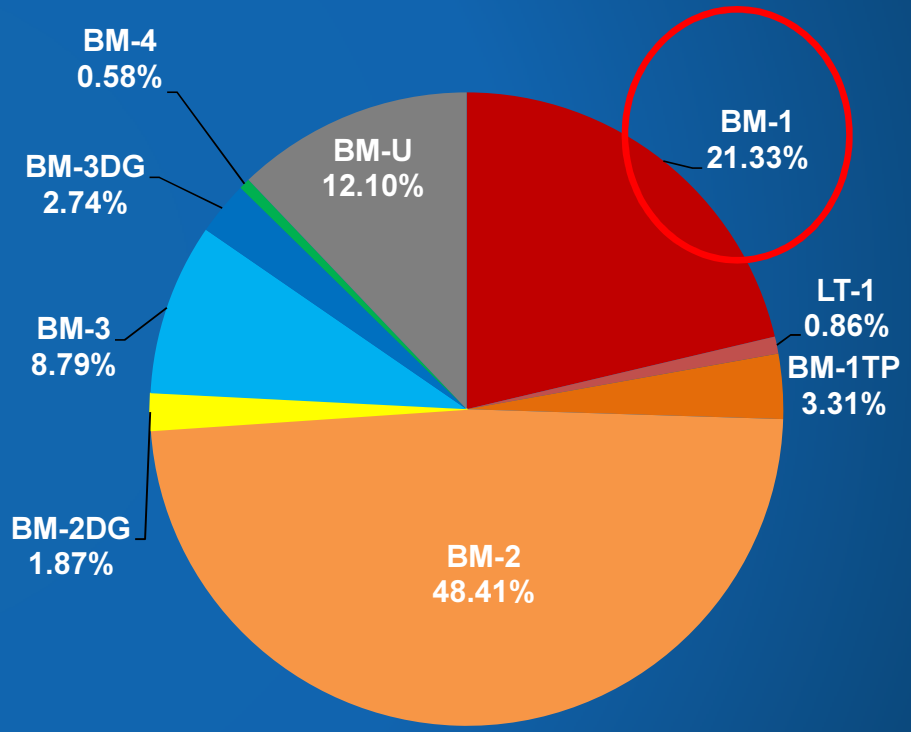
e. High T (Group I Human)

Avoid—Chemical of High Concern

Chemical Name	GreenScreen Benchmark	Rationale
Benzene	1- Red	1e. High T (Carcinogenicity, Mutagenicity/Genotoxicity, Reproductive Toxicity, and Developmental Toxicity)

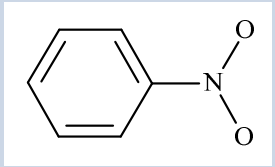
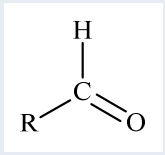
Project Overview

- **Aim:** Identify the structural alerts for Benchmark 1 chemicals (Chemicals of High Concern)
- **Fact:** To date, approximately 21% of GreenScreened chemicals are classified as Benchmark 1 chemicals
- **Issue:** Conducting GreenScreens require toxicological expertise and are time-consuming



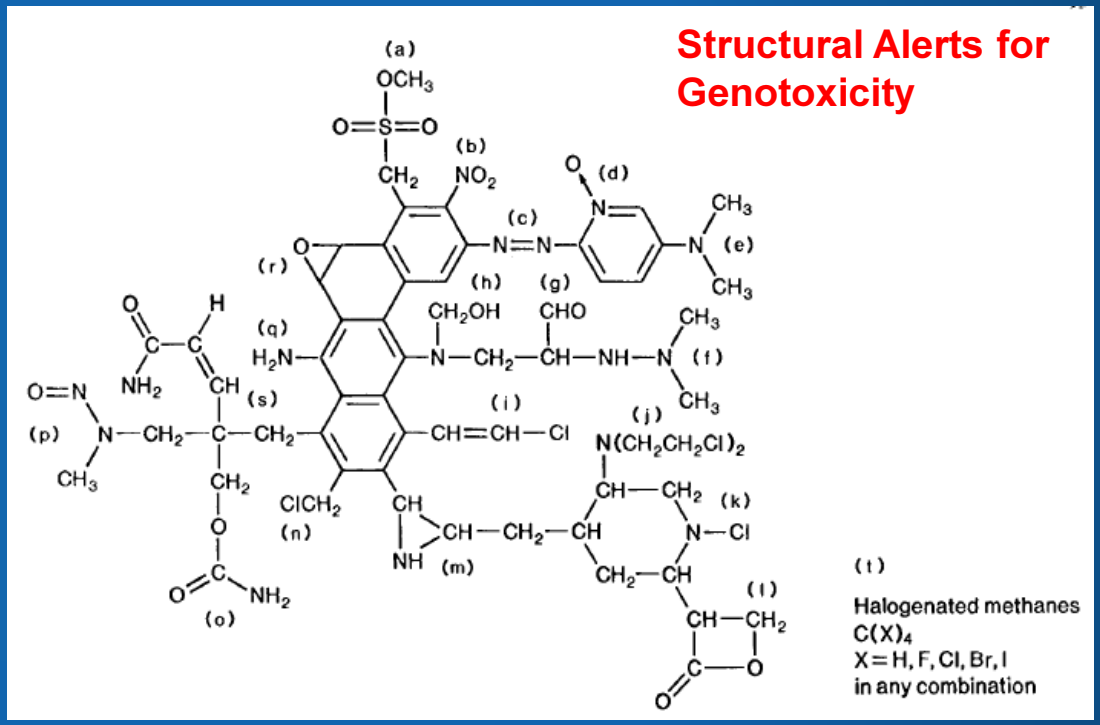
Overview of Structural Alerts

- Chemical Classes, Functional Groups, or Substructures that are likely to lead to a particular toxic effect
- A few articles are publically available that have identified structural alerts for specific hazard endpoints

Reference	Toxic Effect	Example of Structural Alert
Ashby & Tennant 1988, 1989	Genotoxicity	
Payne & Walsh 1994	Skin Sensitization	
Grandjean & Landrigan 2006, 2014	Developmental Neurotoxicity	

Ashby and Tennant

- In toxicology, the Ashby and Tennant composite structure for genotoxic alerts is well-known
  - Easily depicts potential genotoxins, and is useful for carcinogenicity prediction
- In a manner similar to Ashby and Tennant, Identify an overall structure useful for predicting Benchmark 1 chemicals (i.e., chemicals with significant human health and environmental hazards)
- A structure for Benchmark 1 chemicals would be helpful during the product formulation
  - Easily flags potential problematic chemicals



Ashby and Tennant (1988, 1989)

Materials

- 146 Chemicals: Benchmark 1 Chemicals Evaluated by ToxServices
  - Criteria for inclusion in the final data set:
    - Full GreenScreen reviews
    - Finalized prior to December 1, 2015
    - Performed after January 1, 2013
    - Excluded inorganics
    - Chemicals with known structures
- 95 Benchmark 1 Chemicals for Final Review

Methods

- Compiled 95 Benchmark 1 chemicals into a Excel spreadsheet to create a matrix
  - Chemical structures
    - Retrieved from GreenScreens
    - Retrieved from ChemIDplus
  - Hazards
  - Sub-benchmark
- Functional groups of every chemical were analyzed for well-known global structural alerts
  - E.g., halogenated compounds
- Chemicals were assigned to chemical classes
- The matrix was filtered by chemical class
  - Determined that specific chemical classes could be grouped together
- Groups of chemical classes evaluated for patterns
  - Toxicity similarities in the 18 endpoints
  - Sub-benchmarks patterns

Preliminary Organization of Possible Structural Alerts

Hazard Endpoint

Chemical Name	Group I Human					Group II and II* Human									Ecotox		Fate		Physical		Chemical Class
	C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F	
							single	R*	single	R*											
Chemical 1	L	L	M	M	DG	*H*	M	*H*	DG	DG	*H*	DG	*H*	*H*	*H*	*H*	*vH*	*vL*	*vH*	M	**Methacrylic esters (based on monomers structures)**
Chemical 2	*L*	*L*	*M*	*M*	DG	*vH*	*M*	*M*	DG	DG	*H*	DG	*H*	*H*	*M*	***H***	*vH*	*L*	*vH*	*M*	**Methacrylic esters and amide (based on monomers structures)**
Chemical 3	*M*	**L**	**L**	**L**	*M*	**L**	**H**	**M**	*M*	DG	**L**	DG	**M**	*M*	**vH**	**H**	**vL**	**vH**	*L*	*L*	**Methacrylic esters**
Chemical 4	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	**vH**	**vH**	*vH*	*M*	*NA*	*NA*	**Methacrylic esters salts (Zinc)**
Chemical 5	**M**	*L*	*L*	*L*	*DG*	**L**	*M*	*L*	*DG*	*L*	**L**	*DG*	**L**	**M**	**H**	*vH*	*vH*	*vL*	*vH*	**L**	**Methacrylic esters and ethers**

Preliminary Organization of Possible Structural Alerts

Sub-Benchmark

Structural Alerts	Chemical Class	Chemical Name	Sub-Benchmark
Methacrylic Esters	Methacrylic Esters (based on monomers structures)	Chemical 1	1C
	Methacrylic Esters and Amide (based on monomers structures)	Chemical 2	1C
	Methacrylic Esters	Chemical 3	1D
	Methacrylic Acid, Zinc Salt	Chemical 4	1C
	Methacrylic Esters and Ethers	Chemical 5	1C

Results

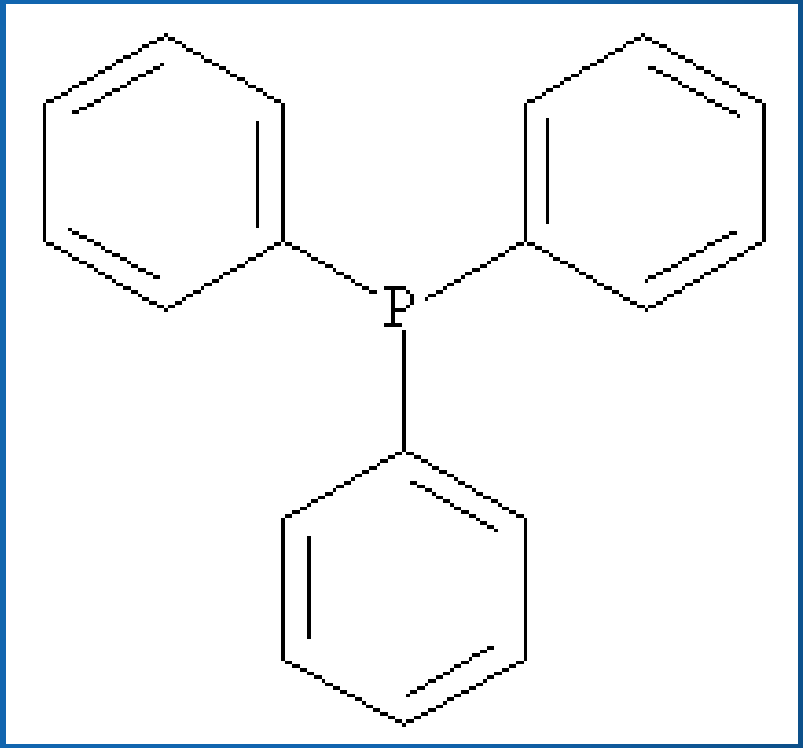
- 11 Potential Structural Alerts (SA) identified
- These are potential alerts due to the relatively low number of chemicals in each potential SA group
- Further analysis will be required to confirm these results

Results – Potential SAs

Potential Structural Alert	Number of Chemicals Within SA
Aromatic Organophosphorus	4
Azo Compounds	18
Benzene Substituted Alkyl, Alkyl Ether, Alkyl Halide and Alcohol	4
Bisphenol and Phenol Derivatives	7
Carboxylic Acid Derivatives of Carbon Chain Length Above Five	6
Compounds with Platinum	2
Compounds with Zinc	4
Cyclosiloxane Derivatives	3
Methacrylic Esters	5
Naphthalene Derivatives	13
Nitrogen Heterocyclic Aromatic Compounds	6

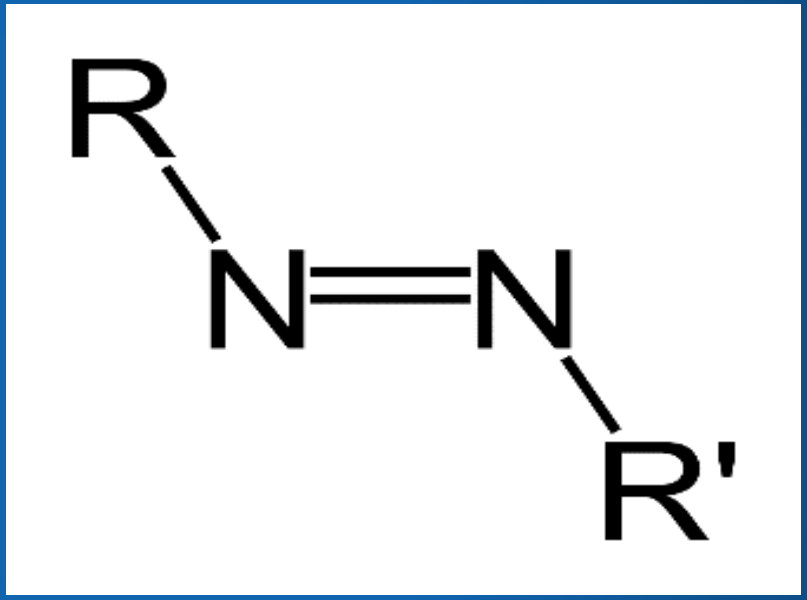
Aromatic Organophosphorus

- Associated with:
  - High to Very High
    - Chronic Aquatic Toxicity
    - Persistence
- Possible Benchmark 1C (vPT)



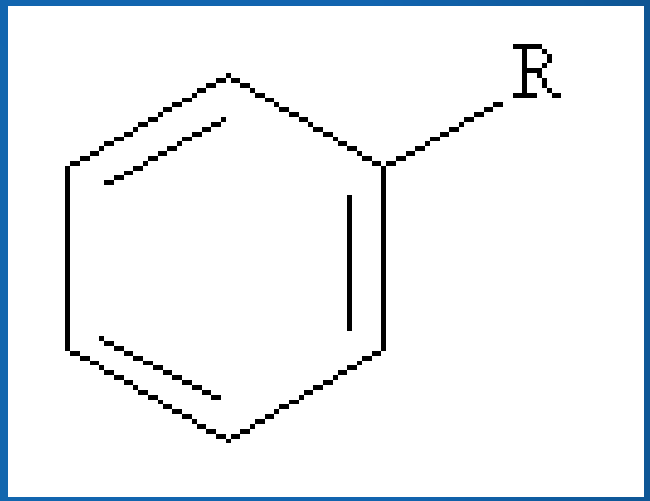
Azo Compounds

- Associated with:
  - Very High
    - Persistence
  - High
    - Skin Sensitization
- Possible Benchmark 1C (vPT)



Benzene Substituted Alkyl, Alkyl Ether, Alkyl Halide and Alcohol

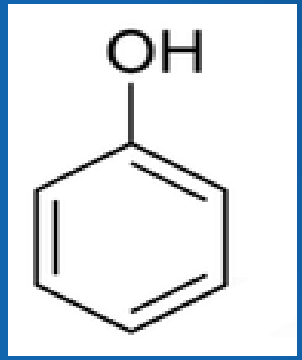
- Aromatic compounds within the dataset, but only those that had a substituted benzene ring were included in this alert group.
- Associated with:
  - High
    - Carcinogenicity
- Possible Benchmark 1E (High T)

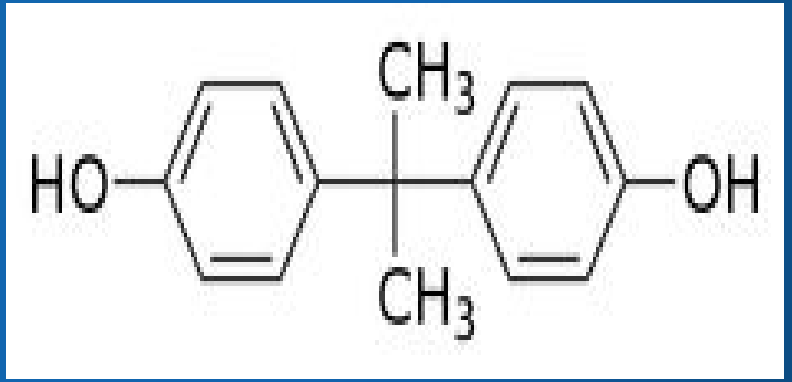


Where R= alkyl, ether, alkyl halide or alcohol

Bisphenol and Phenol Derivatives

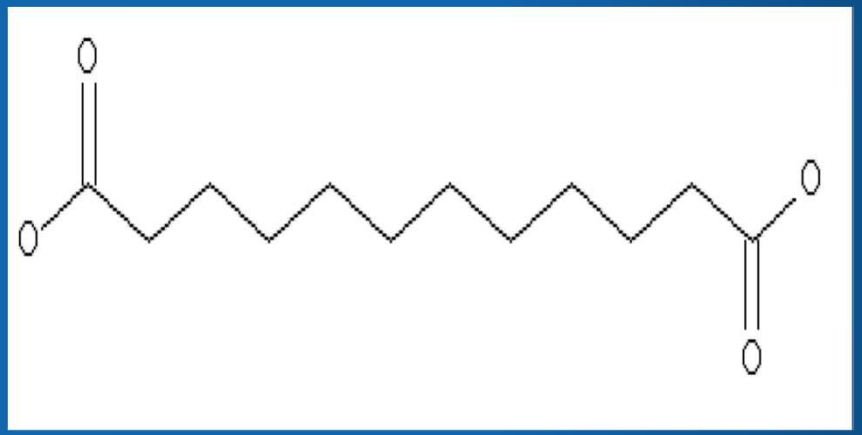
- Associated with:
  - High
    - Carcinogenicity
    - Developmental Toxicity
    - Endocrine Activity
- Possible Benchmark 1E (High T)





Carboxylic Acid Derivatives of Carbon Chain Length Above Five

- Associated with:
  - High to Very High
    - Eye Irritation
    - Acute Aquatic Toxicity
    - Chronic Aquatic Toxicity
    - Persistence
- Possible Benchmark 1C (vPT)



Compounds with Platinum

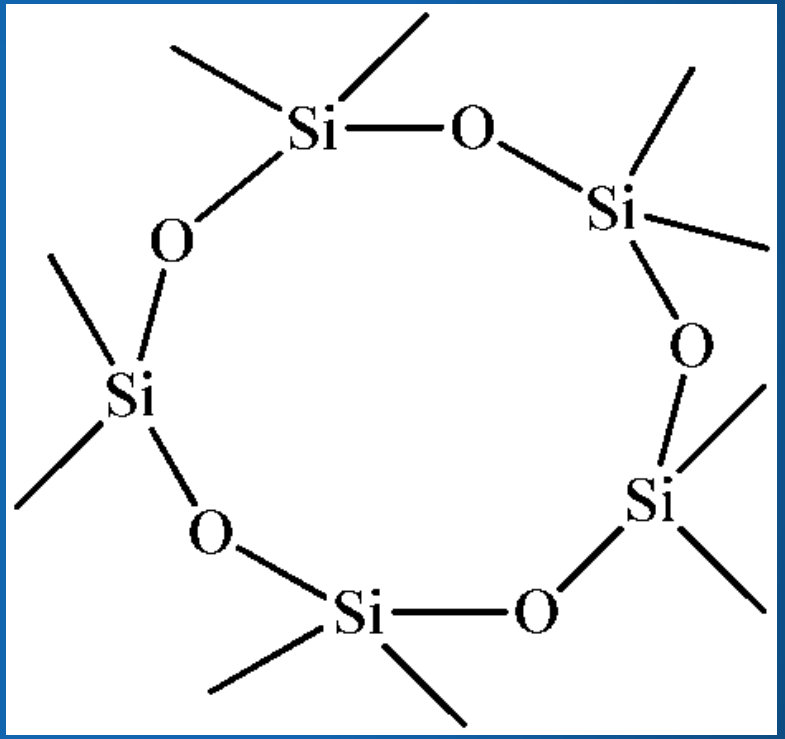
- Associated with:
  - Very High
    - Eye Irritation
    - Persistence
    - Bioaccumulation
  - High
    - Skin Sensitization
    - Respiratory Sensitization
    - Skin Irritation
- Possible Benchmark 1A (PBT), 1B (vPvB), 1C (vPT) , and 1D (vBT)

Compounds with Zinc

- Associated with:
  - Very High
    - Persistence
  - High to Very High
    - Acute Aquatic Toxicity
    - Chronic Aquatic Toxicity
- Possible Benchmark 1C (vPT)

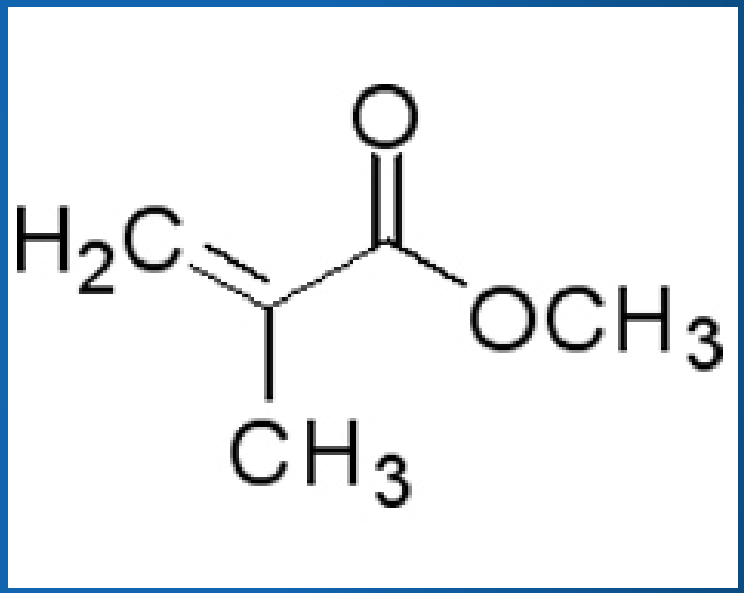
Cyclosiloxane Derivatives

- Associated with:
  - Very High
    - Chronic Aquatic Toxicity
    - Persistence
    - Bioaccumulation
- Possible BM 1A (PBT), 1B (vPvB), 1C (vPT), and 1D (vBT)



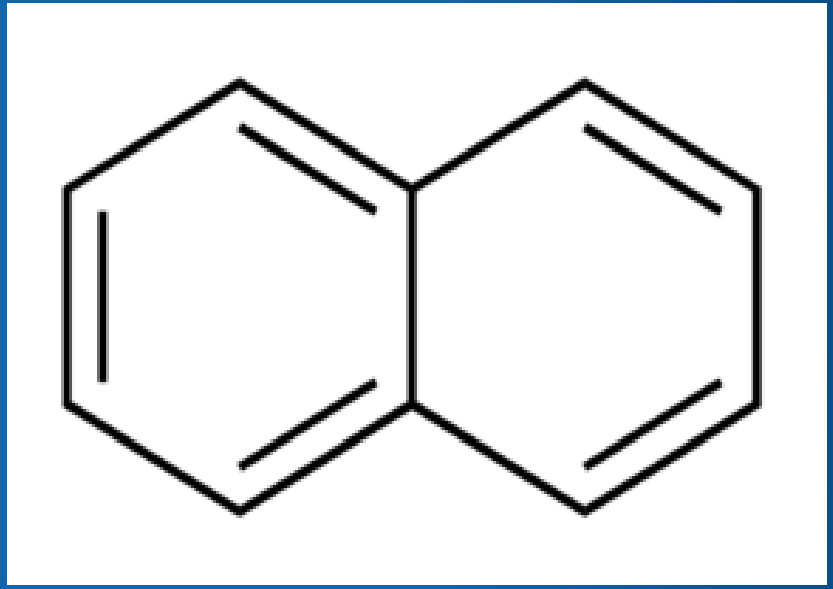
Methacrylic Esters

- Associated with:
  - Very High
    - Persistence
  - High to Very High
    - Acute Aquatic Toxicity
    - Chronic Aquatic Toxicity
- Possible Benchmark 1C (vPT)



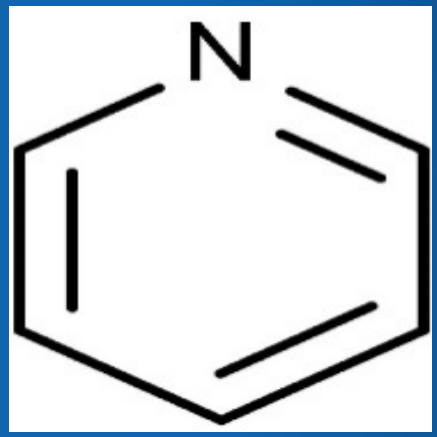
Naphthalene Derivatives

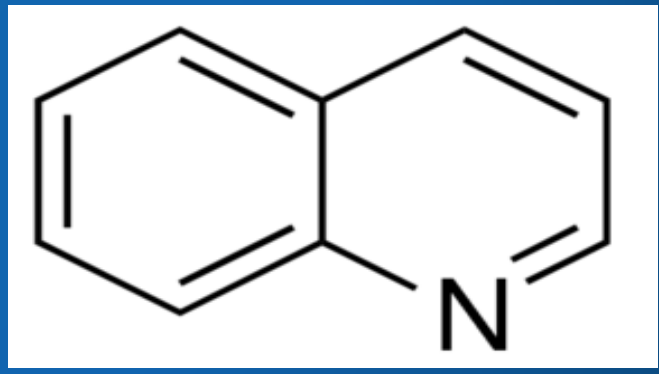
- Associated with:
  - Very High
    - Bioaccumulation
  - High to Very High
    - Eye Irritation
    - Skin Irritation
    - Acute Aquatic Toxicity
    - Chronic Aquatic Toxicity
- Possible Benchmark 1D (vBT)



Nitrogen Heterocyclic Aromatic Compounds (Pyridine and Quinolone Derivatives)

- Associated with:
  - Very High
    - Chronic Aquatic Toxicity
    - Acute Aquatic Toxicity
  - High to Very High
    - Eye Irritation
    - Persistence
    - Bioaccumulation
- Possible Benchmark 1A (PBT)





Future Goals

- Expand the data set to evaluate additional Benchmark 1 chemicals
  - Verify the potential structural alerts identified in this project
  - Identify further potential structural alerts
- Compare the preliminary set of potential structural alerts to Benchmark 2, 3, and 4 chemicals that are in the same chemical class
  - Further verify structural alerts
  - Potentially identify more specific features within the Benchmark 1 structural alerts
- Create multiple composite structures containing structural alerts for organic, organometallic, and polymer Benchmark 1 chemicals
- Compare the function of chemicals versus potential structural alerts

References

- Ashby, J., and Tennant, R. W. (1988). Chemical structure, Salmonella mutagenicity and extent of carcinogenicity as indicators of genotoxic carcinogenesis among 222 chemicals tested in rodents by the U.S. NCI/NTP. *Mutation Research/Genetic Toxicology, 204*(1), 17-115. Retrieved December, 2015.
- Ashby, J., Tennant, R., Zeiger, E., & Stasiewicz, S. (1989). Classification according to chemical structure, mutagenicity to Salmonella and level of carcinogenicity of a further 42 chemicals tested for carcinogenicity by the U.S. National Toxicology Program. *Mutation Research/Genetic Toxicology, 223*(2), 73-103. Retrieved December, 2015.
- Cleaner Production Action. (2013). GREENSCREEN® FOR SAFER CHEMICALS CHEMICAL HAZARD ASSESSMENT PROCEDURE. Retrieved December, 2015, from http://www.cleanproduction.org/static/ee_images/uploads/resources/GreenScreenv1-2_Guidance_Assessment_Procedure_FINAL_2013_9_18.pdf
- All GreenScreen Benchmark Scheme, Criteria, and Method information and images.
- Mittal, K. L., & Fendler, E. J. (2013). *Solution behavior of surfactants: Theoretical and applied aspects* (Vol. 2). Place of publication not identified: Springer. Pg. 171
- M. P. Payne and P. T. Walsh (1994). Structure-activity relationships for skin sensitization potential: Development of structural alerts for use in knowledge-based toxicity prediction systems *Journal of Chemical Information and Computer Sciences*, *34* (1), 154-161. Retrieved December, 2015.
- Grandjean P, Landrigan PJ. Neurobehavioural effects of developmental toxicity.*The Lancet Neurology*. 2014;13(3):330-338. doi:10.1016/S1474-4422(13)70278-3. Retrieved December, 2015.

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Thank you!

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