MA Flame Retardants Law, 2020

An Act to Protect Children, Families and Firefighters from Harmful Flame Retardants

Mass. Gen. Laws Ch 21A, Section 28

TURI
TOXICS USE REDUCTION INSTITUTE
UMASS LOWELL

Which subclasses remain?

- Subclass 1 – Polyhalogenated organophosphates
- Subclass 2 – Polyhalogenated diphenyl ethers
- Subclass 3 – Polyhalogenated alicycles
- Subclass 4 – Polyhalogenated phthalates/benzoates/imides
- Subclass 5 – Polyhalogenated bisphenol aliphatics
- Subclass 6 – Polyhalogenated aliphatic chains
- Subclass 7 – Inorganic (not a NAS subclass)

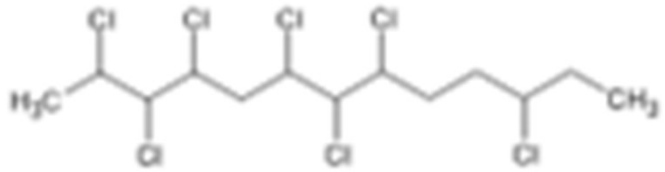
Subclass 6 – Polyhalogenated Aliphatic Chains

AKA:

Short chain chlorinated paraffins (SSCP)

Chloroparaffins

“Polychlorinated alkanes, C10-13” (on TURA list, never reported)



Short chain chlorinated paraffins
85535–84–8
CxH(2x-y+2)Cly
(where x = 10-13; y = 3-12)

General toxicity issues: PBT, aquatic toxicity, carcinogenicity

Proposed Analogues to SCCPs

Medium chain chlorinated paraffins – C14-17

Long chain chlorinated paraffins - C>17

- All 40-70% Cl by wt
- All exist as a mixture of chain lengths

Q3a: Do medium and long chain chlorinated paraffins meet the analogue definition? (i.e., are they analogues of SCCPs?)

Chemical Analogue: A compound having a structure similar to that of another compound, but differing from it in respect to a certain aspect. It can differ in one or more atoms, functional groups, or substructures, which are replaced with other atoms, groups, substructures, or in their arrangement.

Analogue definition from the proposed regulations (developed by DEP, ORS and TURI)

If yes, then:

- Q3b: Are medium and long chain chlorinated paraffins sufficiently similar to short chain chlorinated paraffins such that they would be reasonably anticipated to have similar concerns re: toxic hazard, persistence, bioaccumulation?

The Chloroparaffin Resources

Short:	NTP (1986) – reasonably anticipated to be human carcinogens IARC (1990) – sufficient evidence in animals for C12, 60% Cl, Group 2B ECHA SVHC (2008) - meets vPvB and T (aquatic) EPA TSCA Action Plan for SCCPs (2009) – highly toxic to aquatic invertebrates, P and B (2014 SNUR) UNEP/Stockholm Convention (2016) – list on POPs 2017 Kobetičová (2018): Ecotoxicity assessment of short- and medium-chain chlorinated paraffins
Medium:	EPA TSCA review (2015) of medium and long, notes aquatic toxicity and vP, vB Kobetičová (2018): Ecotoxicity assessment of short- and medium-chain chlorinated paraffins EU (UK) review of medium (2019) – meets vPvB and T (aquatic) ECHA SVHC (2021) – meets vPvB and T (aquatic) UNEP/Stockholm Convention (2023) currently under evaluation for POPs
Long:	NTP (1986) – C23, clear evidence of carcinogenicity for male mice EPA TSCA review (2015) of medium and long, notes aquatic toxicity and vP, vB EU (UK) review of long (2022) – P based on read-across from MCCP, B for C18-C25 with 42-49% Cl, insufficient data for T determination.

	Toxicity Carcinogenicity	Toxicity Aquatic	Persistence	Bioaccumulation
Short Chain	IARC 2B for C12, 60%Cl NTP "reasonably anticipated to be carcinogenic to humans"	Daphnia magna **21-day NOEC = 0.005 mg/l**. Mysidopsis bahia **NOEC = 0.007 mg/l**. (solubility 0.15-0.47 mg/L) (ECHA 2008)	Half-life (days, aerobic) 1630 in freshwater sediment 450 in marine sediment (ECHA 2008)	BCF = 7,273 and 7,816 (ECHA 2008)
Medium Chain	The carcinogenic potential of MCCPs is expected to be similar – at least in qualitative terms – to that of SCCPs, although direct read across is not appropriate. (UK 2019)	Daphnia magna **48h EC50 = <6.5-2200 ug/L; 21-day NOEC =~4-15.6 ug/L** (ECHA 2021)	Total water-sediment DT50 values for MCCP are > 120 days at 12°C (under aerobic conditions) therefore assume degradation half-lives >180 days. (ECHA 2021)	Based on the weight of evidence of the data available, it can be concluded that MCCP have B and/or vB in accordance with REACH Annex XIII. (ECHA 2021)
Long Chain	IARC assigned LCCPs as Class 3 based on malignant lymphomas reported in male mice at very high (5000 mg/kg/day) doses. The registration dossier assigns a Carc. 2 classification H351 (Suspected of causing cancer) under classification and labelling. (UK 2022)	Using estimated environmental concentrations, MCCP and LCCP may present an unreasonable risk following acute and chronic exposures to aquatic organisms. (EPA 2015)	In the absence of information on specific congener groups and data for MCCP or LCCP products, EPA/OPPT concludes that at least some congener groups present in both MCCP and LCCP products are persistent to very persistent (EPA 2015)	In the absence of information on specific congener groups and data for MCCP or LCCP products, EPA/OPPT concludes that at least some congener groups present in both MCCP and LCCP products are bioaccumulative to very bioaccumulative based on multiple lines of evidence including: Log KOW values, modeled BCFs, laboratory-measured BCFs, field-measured BAFs, field-measured biomagnification factors (BMFs), laboratory-measured biota-sediment accumulation factors (BSAFs) and the presence of MCCPs and LCCPs in human and wildlife biota. (EPA 2015)

Q3b: Are medium and long chain chlorinated paraffins sufficiently similar to short chain chlorinated paraffins such that they would be reasonably anticipated to have similar concerns re: toxic hazard, persistence, bioaccumulation?

Predictive Tools and how we used them

- CompTox - FR Lists
- CompTox - GenRA
- CompTox - Physical/Chemical Properties
- CompTox - ToxValDB
- CompTox - ToxCast
- CompTox - PubMed
- Cheminformatics
- EpiSuite (BioWIN)
- QSAR - OECD

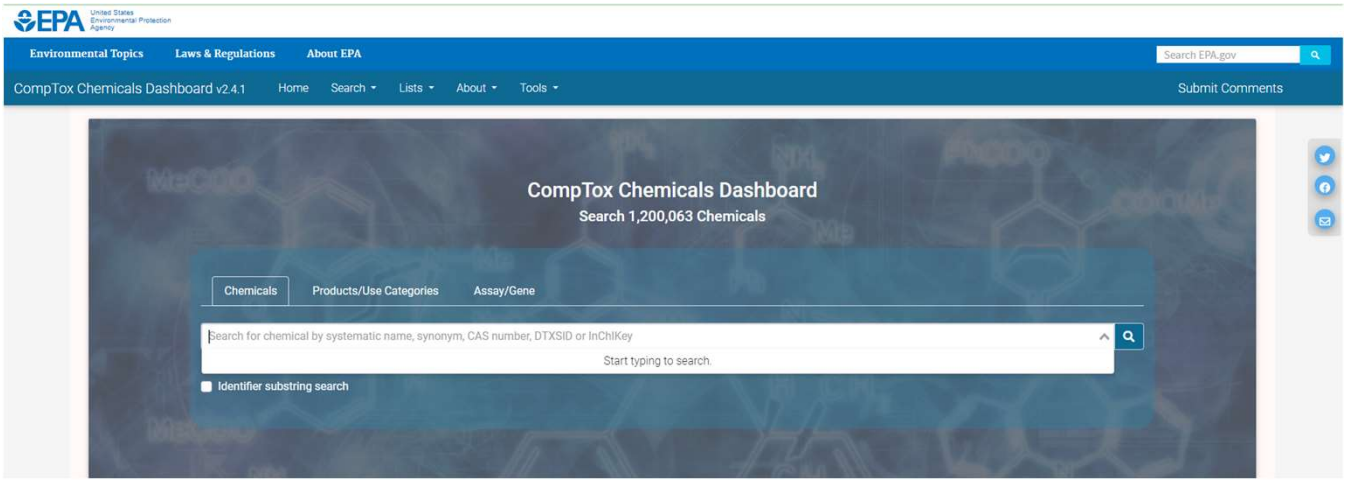
How we chose analogues

- Chemical Analogue definition (DEP/TURI): A compound having a structure similar to that of another compound, but differing from it in respect to a certain aspect. It can differ in one or more atoms, functional groups, or substructures, which are replaced with other atoms, groups, substructures, or in their arrangement.

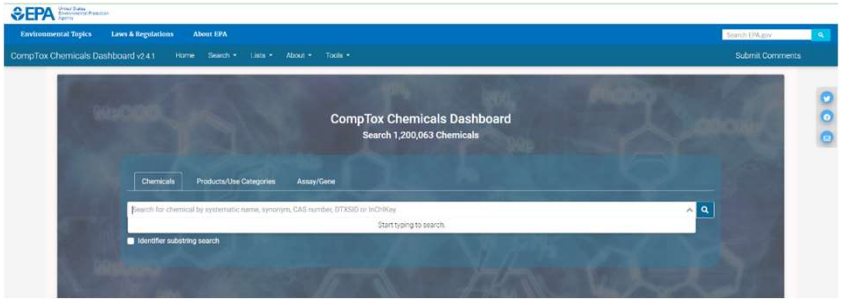
- Reviewed reports from more than 30 organizations (universities, NGOs, governments) that have studied FRs, identified a list of approx. 200 FRs, visually identified structurally similar chemicals to the 11 in the law, considered possible use in the product categories, chose very closely related analogues for SAB consideration

CompTox – Computational Toxicology (EPA)

- FR Lists
- GenRA
- Physical/Chemical Properties
- ToxValDB
- ToxCast
- PubMed



CompTox – FR Lists

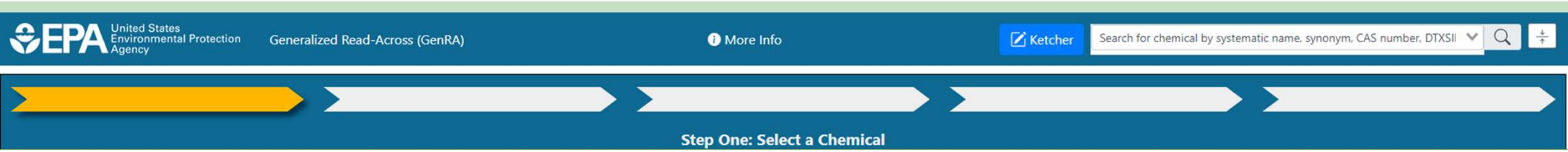


List Acronym	List Name	# of Chemicals	List Description
FLAMERETARD	CATEGORY: Flame Retardants	760	List of Flame Retardants including all polybrominated diphenyl ethers (PBDEs). Sources include the Wikipedia Flame Retardants list and a text-mining exercise using MeSH identifiers
FRFULLLIST	CATEGORY: Flame Retardants - US CPSC/US EPA Flame Retardant Inventory	797	Joint US Consumer Product Safety Commission (CPSC)-US Environmental Protection Agency (EPA) Flame Retardant Inventory: potential Flame Retardant substances identified from publicly-available materials. This encompasses EPA/CPSC reports, published literature, as well as publicly available information from manufacturers. For more information on the collection and curation process see the published article [Nature Scientific Data DOI will be inserted when available] and the published dataset [Figshare DOI for final dataset will be inserted when available].
FRLIKELY	CATEGORY: Likely Flame Retardants - Partial subset of the US CPSC/US EPA Flame Retardant Inventory	746	Likely Flame Retardants: A subset of the Joint US CPSC-US EPA Flame Retardant Inventory of substances that have undergone review by a panel of experts and have been identified as being likely flame retardants. In addition to expert opinion, substances' flame retardancy were predicted with Quantitative Structure-Use Relationships (see Phillips, et al, 2017 for more information on this methodology).
OFRLIKELY	CATEGORY: Likely Organohalogen Flame Retardants - Partial subset of the US CPSC/US EPA Flame Retardant Inventory	489	Likely Organohalogen Flame Retardants: A subset of the Join US CPSC-US EPA Flame Retardant Inventory of substances that have undergone review by a panel of experts and have been identified as being likely organohalogen flame retardants (i.e., substances that are likely flame retardants and have at least one Carbon-Halogen bond). In addition to expert opinion, substances' flame retardancy and organohalogen structure were bolstered by use of Quantitative Structure-Use Relationships (see Phillips, et al, 2017 for more information on this methodology).
PBDES	CATEGORY: Polybrominated diphenyl ethers (PBDEs)	209	A list of all 209 polybrominated diphenyl ethers, many of which, in mixture form, are flame retardants

Can search lists individually or do a batch search (many chemicals, all FR lists); "last updated" is also a field, mostly 2022 for these lists

CompTox: GenRA – Generalized Read-Across - EPA

- "An algorithmic approach to permit objective and reproducible read-across predictions of *in vivo* toxicity and *in vitro* bioactivity"
- Have a target chemical, looking for "analogues" (called candidate source analogues) to help fill data gaps in the target and its "analogues"
- "Analogues" are first identified, evaluated, and then data gap filling is performed using GenRA's similarity weighted activity approach
- Structural and bioactivity information or a combination of both can be used to identify "analogues" with available *in vitro* bioactivity and/or *in vivo* toxicity data.



GenRA – to search for “analogues”

Chemical similarity:

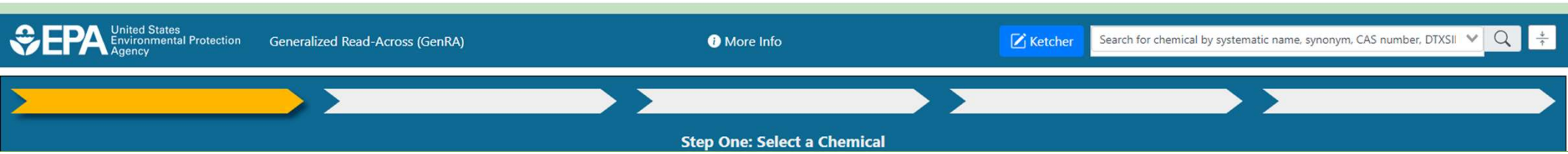
- Morgan Fingerprints - most popular, AKA extended connectivity, best for small molecules, presences of specific substructures around each atom, predictive of biological activity
- Torsion Fingerprints - topological relationships between bonds in a molecule
- **ToxPrints - chemically informative atom/ring/chain/bond features**
- AIM - Analog Identification Methodology structural analysis of atoms, groups, super fragments

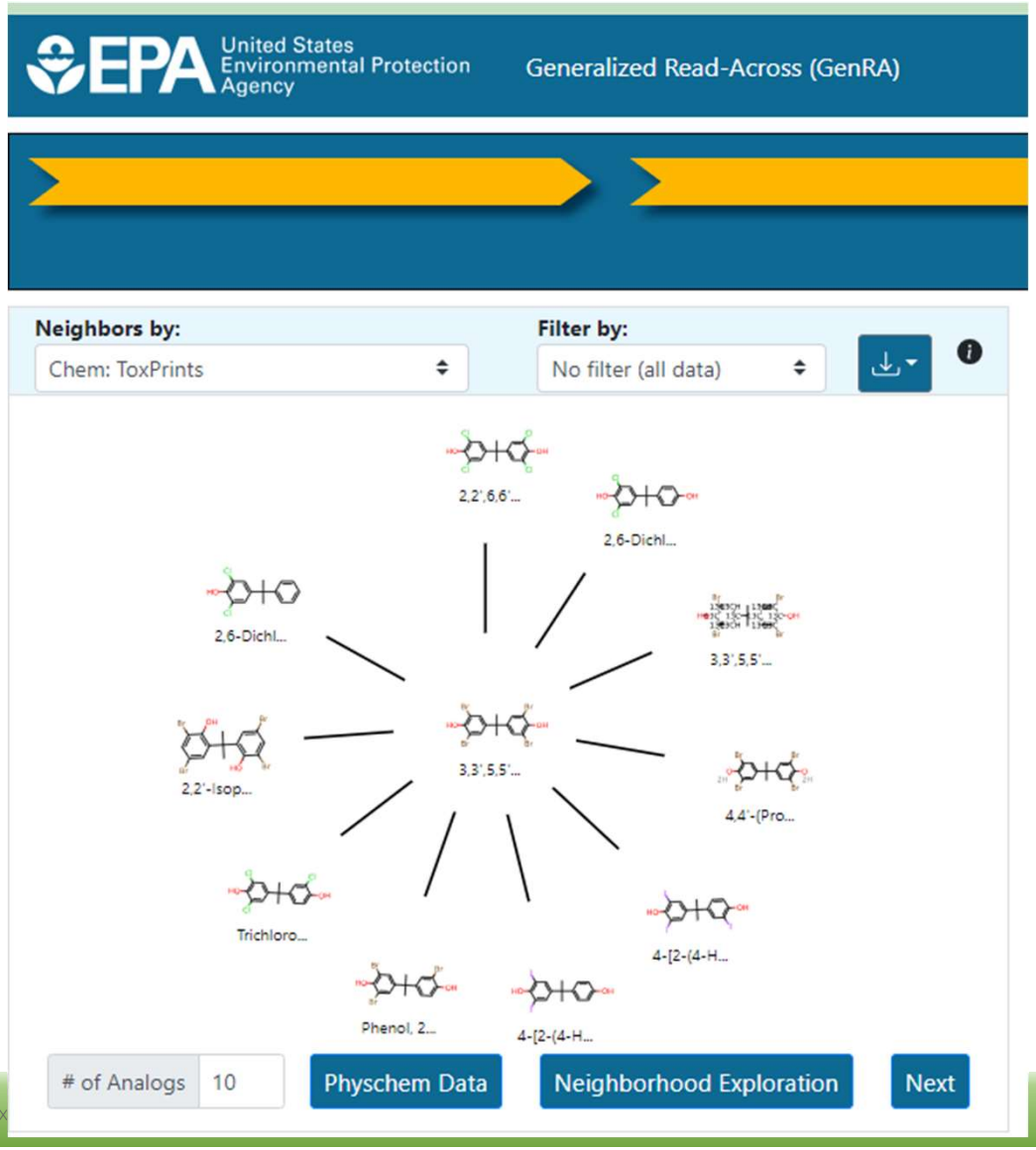
Biological similarity:

- ToxCast - bioactivity assay data
- ToxRef - in vivo studies

Cool features:

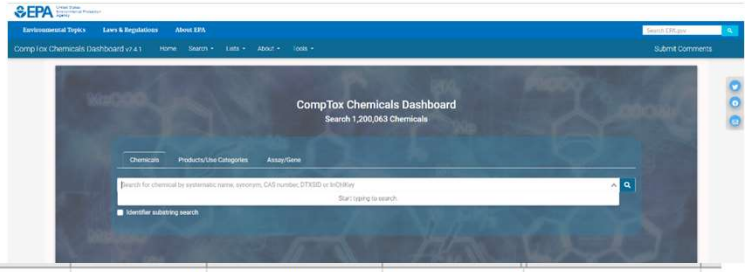
- Compare physicochemical properties on a chart to see how similar they are
- See data gaps





- Example for TBBPA using ToxPrints similarity and using all data.
- Shows top 10 similar chemicals
- We used top 100 then cross referenced with FullFR list – 3 matches:
  - 1 - was the analogue we chose, tetrachlorobisphenol A
  - 2 - no evidence of use as an FR (PubChem,"use" and patents)
- Tool can show data gaps then predict in vivo toxicity and in vitro bioactivity

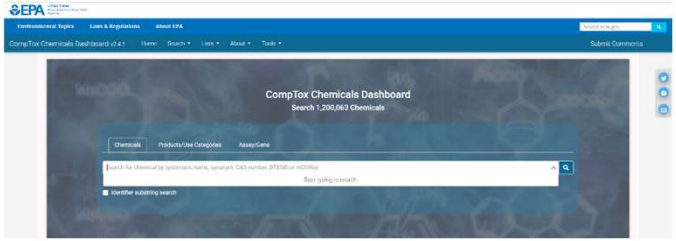
CompTox – Physical/Chemical Properties and Environmental Fate and Transport



- We provided these for every chemical/analogue
- Most data are predicted
- Can see source (e.g., OPERA) for each record
- Challenge to incorporate experimental data
- Example for TBB

Property	Experimental average	Predicted average	Experimental median	Predicted median	Experimental range	Unit
Polarizability	-	40.1 (1)	-	40.1	-	Å^3
Henry's Law	-	7.41e-4 (1)	-	0.000741	-	atm-m3/mole
Boiling Point	-	431 (4)	-	434	-	°C
Flash Point	-	230 (2)	-	230	-	°C
Melting Point	-	122 (3)	-	148	-	°C
Molar Refractivity	-	101 (1)	-	101	-	cm^3
Molar Volume	-	308 (1)	-	308	-	cm^3
Viscosity	-	46.5 (1)	-	46.5	-	cP
Surface Tension	-	43.3 (1)	-	43.3	-	dyn/cm
Density	-	2.01 (2)	-	2.01	-	g/cm^3
LogD5.5	-	6.19 (1)	-	6.19	-	Log10 unitless
LogD7.4	-	6.19 (1)	-	6.19	-	Log10 unitless
Vapor Pressure	-	3.57e-7 (3)	-	0.000000113	-	mmHg
Water Solubility	-	7.18e-7 (4)	-	9.01E-08	-	mol/L
Thermal Conductivity	-	119 (1)	-	119	-	mW/(m*K)
Index of Refraction	-	1.57 (1)	-	1.57	-	-
LogKoa: Octanol-Air	-	11.6 (1)	-	11.6	-	-
LogKow: Octanol-Water	-	7.47 (4)	-	7.47	-	-
ReadyBiodeg		0.00 (1)		0		Binary 0/1
Soil Adsorp. Coeff. (Koc)		1.26e+4 (1)		12600		L/kg
Fish Biotrans. Half-Life (Km)		0.245 (1)		0.245		days
Atmos. Hydroxylation Rate		1.38e-11 (1)		1.38E-11		cm3/molecule*sec
Biodeg. Half-Life		3.39 (1)		3.39		days
Bioconcentration Factor		945 (2)		945		L/kg

CompTox: ToxValDB



- CompTox – ToxValDB - a comprehensive collection of quantitative summary data from public data sets. ToxValDB collects data from 34 unique sources including those from the EPA, DOE, DOD, CDC/ATSDR, FDA, ECHA, EFSA, Health Canada, and the California EPA. The data are largely limited to summary values from individual studies or chemical-level assessments, and is focused on quantitative values such as LOAELs, NOAELs, BMDs, LD50s and RfDs.
- Example for TDCPP

More	Priority	Source	Type	Subtype	Risk Assessment	Qualifier	Value	Units	Study Type	Exposure Route	Critical effect	Species	Year
	1	ATSDR MRLs 2020	NOAEL	-	chronic	=	5.00	mg/kg-day	chronic	oral	renal	Human (RA)	2012
	1	ATSDR MRLs 2020	NOAEL	-	chronic	=	2.00	mg/kg-day	chronic	oral	renal	Human (RA)	2012
	1	ATSDR MRLs 2022	NOAEL	-	short-term	=	5.00	mg/kg-day	short-term	oral	renal	Human (RA)	-
	1	ATSDR MRLs 2022	NOAEL	-	chronic	=	2.00	mg/kg-day	chronic	oral	renal	Human (RA)	-
	5	Chiu	BMDL	-	chronic	=	1.94	mg/kg-day	chronic	oral	renal tubular epithelial hyperplasia	Rat	2009
	5	HPVIS	NOAEL	-	chronic	=	5.00	mg/kg-day	chronic	oral	-	Rat	1981
	5	HPVIS	NOAEL	-	developmental	=	100	mg/kg-day	developmental	oral	-	Rat	1978
	5	HPVIS	NOAEL	-	developmental	=	25.0	mg/kg-day	developmental	oral	-	Rat	1978
	5	Wignall	BMDL	-	chronic	=	1.94	mg/kg-day	chronic	oral	renal tubular epithelial hyperplasia;renal tubular epithelial hyperplasia	Rat	1981
	5	Wignall	BMD	-	chronic	=	4.71	mg/kg-day	chronic	oral	renal tubular epithelial hyperplasia;renal tubular e	Rat	1981

CompTox: ToxCast – Toxicity Forecaster (bioactivity)

- **ToxCast** makes *in vitro* medium- and high-throughput screening assay data publicly available for prioritization and hazard characterization of thousands of chemicals

- Example below is for TBPH, Active only

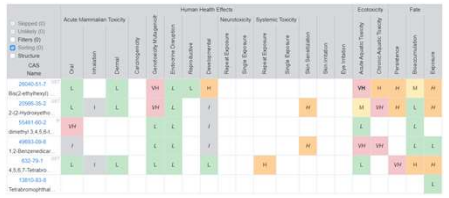
NAME	GENE_SYMB	GENE_NAME	HIT_CA	ASSAY_FUNCTION_	FLAGS	STOCK_CONC	ORGANISM	CELL_LINE	CELL_FORM	INTENDED_TARGE	INTENDED_TARGE	INTENDED_TARGE	BIOLOGICAL_PROC	DETECTION_TECH	TISSUE
BSK_CASM3C_IL6	IL6	interleukin 6	Active	signaling	Less than 50% efficacy,Bmd > ac	14.69999981	human	coronary arter	primary cell	cytokine	protein	interleukins	regulation of gene ex	Fluorescence	vascular
TOX21_PXR_agonist	NR1I2	nuclear receptor s	Active	agonist	Less than 50% efficacy	20	human	HepG2	cell line	nuclear receptor	protein	non-steroidal	regulation of transcri	Luminescence	liver
TOX21_GR_BLA_Agonist_ch2	-	-	Active	product	Only highest conc above baseline	20	human	HeLa	cell line	channel 2	pathway	baseline control	regulation of transcri	Fluorescence	cervix
CCTE_Shafer_MEA_dev_network_spike_pe	-	-	Active	electrical activity	Less than 50% efficacy,Bmd > ac	20	rat	primary cortic	primary cell	neurodevelopment	extracellular	neural network functi	functional neural net	microelectrode array	cortical
TOX21_AR_LUC_MDAKB2_Agonist	AR	androgen receptor	Active	agonist	-	20	human	MDA-kb2	cell line	nuclear receptor	protein	steroidal	regulation of transcri	Luminescence	breast
BSK_CASM3C_SAA	SAA1	serum amyloid A1	Active	signaling	Less than 50% efficacy,Average n	14.69999981	human	coronary arter	primary cell	cell adhesion molecu	protein	apolipoproteins	regulation of gene ex	Fluorescence	vascular
TOX21_AR_LUC_MDAKB2_Agonist_3uM_N	AR	androgen receptor	Active	agonist	-	20	human	MDA-kb2	cell line	nuclear receptor	protein	steroidal	regulation of transcri	Luminescence	breast
TOX21_PR_BLA_Agonist_ratio	PGR	progesterone rece	Active	ratio	Less than 50% efficacy	20	human	PR-UAS-bla-H	cell line	nuclear receptor	protein	steroidal	regulation of transcri	Fluorescence	kidney
ATG_GR_TRANS	NR3C1	nuclear receptor s	Active	reporter gene	Average number of replicates per	14.69999981	human	HepG2	cell line	nuclear receptor	protein	steroidal	regulation of transcri	Fluorescence	liver
TOX21_GR_BLA_Agonist_ratio	NR3C1	nuclear receptor s	Active	ratio	Less than 50% efficacy	20	human	HeLa	cell line	nuclear receptor	protein	steroidal	regulation of transcri	Fluorescence	cervix
NVS_NR_hGR	NR3C1	nuclear receptor s	Active	binding	Average number of replicates per	14.69999981	human	NA	cell-free	nuclear receptor	protein	steroidal	receptor binding	Radiometry	NA
TOX21_PR_BLA_Agonist_ch2	-	-	Active	product	Less than 50% efficacy	20	human	PR-UAS-bla-H	cell line	channel 2	pathway	baseline control	regulation of transcri	Fluorescence	kidney
BSK_4H_MCP1	CCL2	chemokine (C-C n	Active	signaling	Average number of replicates per	14.69999981	human	umbilical vein	primary cell	cytokine	protein	chemotactic factor	regulation of gene ex	Fluorescence	vascular
CCTE_Shafer_MEA_dev_AB	-	-	Active	cell viability	Less than 50% efficacy,Cell viabili	20	rat	primary cortic	primary cell	cell cycle	cellular	cytotoxicity	cell death	fluorescence	cortical

From CompTox Dashboard can also see Metadata "Number of PubMed Articles" which gives an idea of how much the substance has been studied

Example for the polyhalogenated organophosphate subclass and analogues

Chemical	Number of PubMed articles
TDCPP	337
Brominated Tris	223
Tris(tribromoneopentyl) phosphate	3
Bis(2,3-dibromopropyl) phosphate	15
TCEP	1119
Bis(2-chloroethyl)2-chloroethylphosphonate	2
V6	0
TCPP	227

Cheminformatics (EPA)



- These modules provide information on chemical structures, experimental and predicted physicochemical properties, environmental fate and transport information, and appropriately linked toxicity data (using QSAR and empirical)

- NOTE: the Cheminformatics Tool is a beta version and under development

- We used the Hazard Comparison Dashboard which arrays the data against the typical toxicity outcomes using a combination of QSAR models and empirical data - can view the summary table and/or the raw data

- Score the endpoint VH, H, M, L

Cheminformatics example with TBPH/TBB and analogues

Skipped (0) / Unlikely (0) / Filters (0) / Sorting (0) / Structure	Human Health Effects															Ecotoxicity		Fate		
	Acute Mammalian Toxicity								Neurotoxicity		Systemic Toxicity									
CAS Name	Oral	Inhalation	Dermal	Carcinogenicity	Genotoxicity Mutagenicity	Endocrine Disruption	Reproductive	Developmental	Repeat Exposure	Single Exposure	Repeat Exposure	Single Exposure	Skin Sensitization	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Exposure
26040-51-7 GBT Bis(2-ethylhexyl) ...	L		L		VH	*L*	L	H								**VH**	H	*H*	M	*H*
20566-35-2 GBT 2-(2-Hydroxyetho...	L	I	L		*VH*	*L*		*I*					*H*			M	*VH*	*H*	L	*H*
55481-60-2 M dimethyl 3,4,5,6-t...	*VH*				*L*	*L*		*I*								*L*			*L*	
49693-09-6 1,2-Benzenedicar...	*I*				*L*	*L*		*I*					*H*			*VH*	*VH*		*L*	*L*
632-79-1 GBT 4,5,6,7-Tetrabro...	L	I	L		L	*L*		L			H					L		*VH*	H	*H*
13810-83-8 Tetrabromophthal...																				*L*

Questions from the last meeting

- Does Cheminformatics distinguish between the screening schemes? (i.e., are any trusted more than others?)

  If a source is screening level, it will have the same weighting as any other screening source.

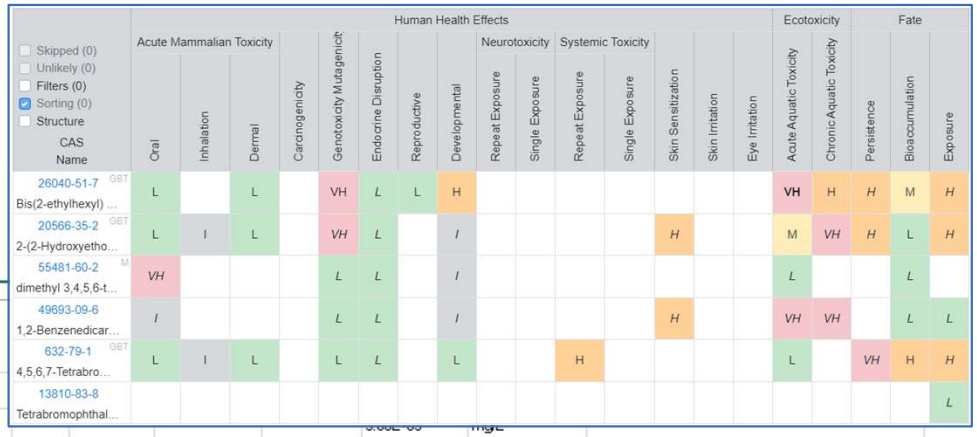
- How is the final score assigned?

  It uses the most hazardous score from the most authoritative source

  3 authority levels:

  1. Authoritative (most authoritative)
  2. Screening
  3. QSAR model (least)

Supporting data for Cheminformatics Scoring



Skipped (0) / Unlikely (0) / Filters (0) / Sorting (0) / Structure	Human Health Effects															Ecotoxicity		Fate		
	Acute Mammalian Toxicity			Carcinogenicity	Genotoxicity Mutagenicity	Endocrine Disruption	Reproductive	Developmental	Neurotoxicity		Systemic Toxicity		Skin Sensitization	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Exposure
CAS / Name	Oral	Inhalation	Dermal						Repeat Exposure	Single Exposure	Repeat Exposure	Single Exposure								
26040-51-7 GBT Bis(2-ethylhexyl) ...	L		L		VH	L	L	H								VH	H	H	M	H
20566-35-2 GBT 2-(2-Hydroxyetho...	L	I	L		VH	L		I					H			M	VH	H	L	H
55481-60-2 M dimethyl 3,4,5,6-t...	VH				L	L		I								L			L	
49693-09-6 1,2-Benzenedicar...	I				L	L		I					H			VH	VH		L	L
632-79-1 GBT 4,5,6,7-Tetrabro...	L	I	L		L	L		L			H					L		VH	H	H
13810-83-8 Tetrabromophthal...																				L

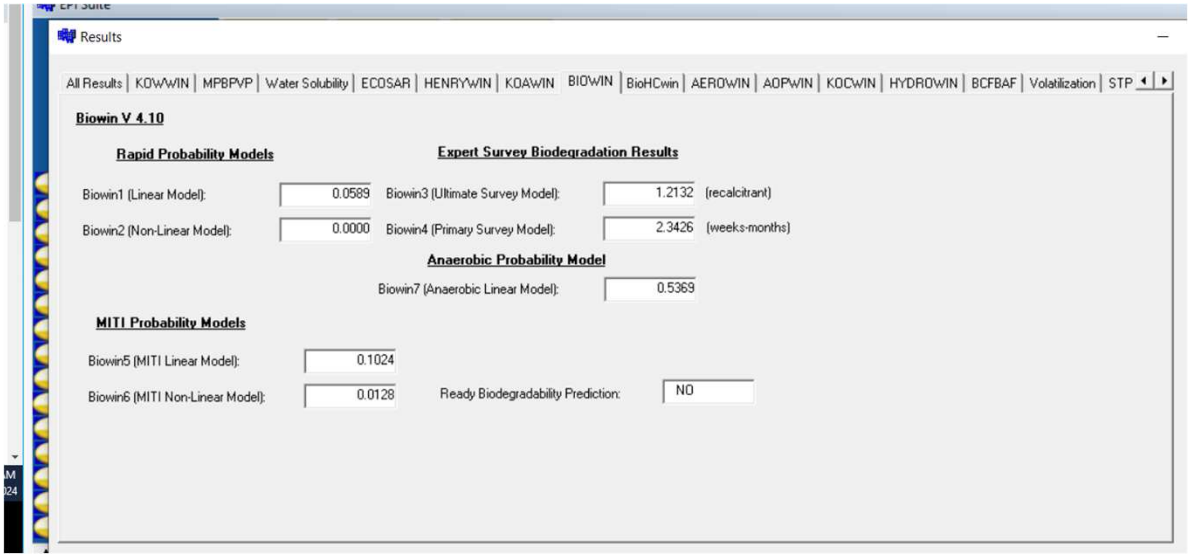
CAS	Source	Original Sourc	List Type	Score	Rationale	Category							
26040-51-7	ToxVal	ECOTOX	Authoritative	VH	LC50 < 1 mg/L								
26040-51-7	TSCA work plan		Screening	H	Score of H was assigned based on a category of Acute aquatic toxicity	Acute aquatic toxicity							
26040-51-7	T.E.S.T. (predicted value)		QSAR Model	VH	96 hr Fathead minnow LC50 (0.003 mg/kg) < 1 mg/L								
26040-51-7	T.E.S.T. (predicted value)		QSAR Model	L	Predicted 96 hour fathead minnow LC50 of 2.20E-02 mg/L is greater than the TEST predicted water solubility of 9.00E-03 mg/L						0.02	mg/L	
26040-51-7	ToxVal	ECHA IUCLID	Screening	I	EC50 does not provide enough information to assign a score		2	days	water flea	EC50	> 10	mg/L	-
20566-35-2	ToxVal	ECHA IUCLID	Screening	M	10 mg/kg < LC50 <=100 mg/L		4	days	bluegill	LC50	12	mg/L	-
20566-35-2	DSL		Screening	L	Score of L was assigned based on a category of "Not Inherently_Toxic_to_Aquatic_Organisms"	Not Inherently_Toxic_to_Aquatic_Organisms							
20566-35-2	T.E.S.T. (predicted value)		QSAR Model	VH	96 hr Fathead minnow LC50 (0.456 mg/kg) < 1 mg/L						0.46	mg/L	
20566-35-2	T.E.S.T. (predicted value)		QSAR Model	H	1 mg/L <= 48 hr Daphnia magna LC50 (1.705 mg/L) <= 10 mg/L						1.71	mg/L	
55481-60-2	T.E.S.T. (predicted value)		QSAR Model	L	Predicted 96 hour fathead minnow LC50 of 1.79E-01 mg/L is greater than the TEST predicted water solubility of 1.26E-01 mg/L						0.18	mg/L	
55481-60-2	T.E.S.T. (predicted value)		QSAR Model	L	Predicted 96 hour fathead minnow LC50 of 6.38E-01 mg/L is greater than the TEST predicted water solubility of 1.26E-01 mg/L						0.64	mg/L	
49693-09-6	T.E.S.T. (predicted value)		QSAR Model	VH	96 hr Fathead minnow LC50 (0.029 mg/kg) < 1 mg/L						0.03	mg/L	
49693-09-6	T.E.S.T. (predicted value)		QSAR Model	L	Predicted 96 hour fathead minnow LC50 of 1.33E-01 mg/L is greater than the TEST predicted water solubility of 4.80E-02 mg/L						0.13	mg/L	
632-79-1	DSL		Screening	L	Score of L was assigned based on a category of "Not Inherently_Toxic_to_Aquatic_Organisms"	Not Inherently_Toxic_to_Aquatic_Organisms							
632-79-1	T.E.S.T. (predicted value)		QSAR Model	N/A	Fathead minnow LC50 (96 hr) could not be predicted using T.E.S.T.								
632-79-1	T.E.S.T. (predicted value)		QSAR Model	N/A	Daphnia magna LC50 (48 hr) could not be predicted using T.E.S.T.								
632-79-1	ToxVal	ECHA IUCLID	Screening	I	LC50 does not provide enough information to assign a score		4	days	bluegill	LC50	> 10	mg/L	-
632-79-1	ToxVal	ECHA IUCLID	Screening	I	EC50 does not provide enough information to assign a score		2	days	water flea	EC50	> 5.60	mg/L	-

EpiSuite (EPA) - BioWIN

- EPI (Estimation Programs Interface) Suite™ is a Windows®-based suite of physical/chemical property and environmental fate estimation programs developed by EPA and Syracuse Research Corp

- Version 4.11 (2017)

Example for PentaBDE



QSAR – Quantitative Structure Activity Relationship (OECD)

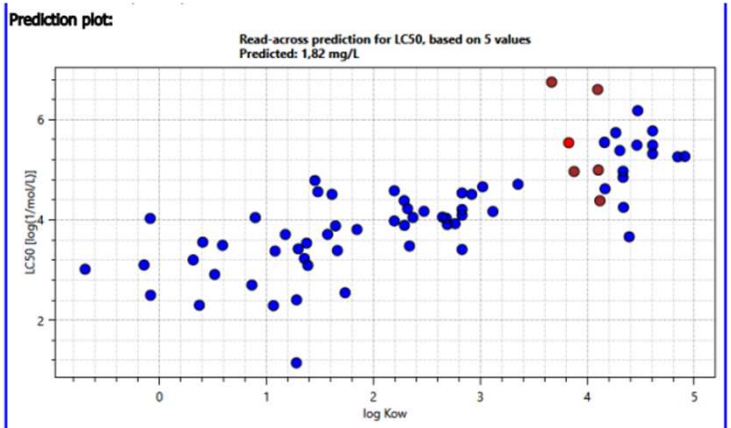
Correlation between chemical structure and associated biological activity, with the ultimate goal of predicting the activity of untested chemicals based on structurally related compounds with known activity

What we tried:

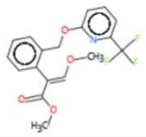
- Fixed endpoints related to aquatic toxicity (LC50) and skin sensitization
- Input analogues to predict data gaps from similar compounds
- Ran aquatic toxicity endpoint for chosen TBPH/TBB/analogues and alicycles/ analogues, all above solubility
- Also looked at metabolites; QSAR has metabolic simulator Oasis embedded

Example for Analogue #1 of TBPH, showing just one of the values used

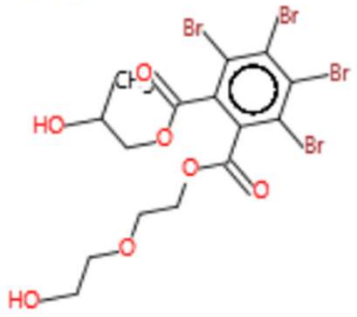
Prediction plot:



Values used for the prediction:

Structure	Experimental values used for the prediction (Arithmetic mean (average))	log Kow
CAS: 117428-22-5 SMILES: CO\C=C(\C(=O)OC)c1ccccc1COc1ccc c(n1)C(F)(F)F Name: Picoxystrobin 	6,75 log(1/mol/L) [0,0655 mg/L]	3,67

Target information

Structural information	Numerical identifiers	Chemical names
SMILES: CC(O)COC(=O)c1c(Br)c(Br)c(Br)c(Br)c1C(=O)OCCOCCO Structure 	CAS#: 20566-35-2 Other: EC Number:2438850	1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1-[2-(2-hydroxyethoxy)ethyl] 2-(2-hydroxypropyl) ester 1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 2-(2-hydroxyethoxy)ethyl 2-hydroxypropyl ester 2-(2-hydroxyethoxy)ethyl 2-hydroxypropyl 3,4,5,6-tetrabromobenzene-1,2-dicarboxylate

Prediction summary

Predicted endpoint: Ecotoxicological Information -> Aquatic Toxicity -> Mortality -> LC50 -> 96 h -> Animalia (animals) -> Chordata (chordates) -> Actinopterygii (ray-finned fishes,spiny rayed fishes) -> Teleostei -> Pimephales promelas

Predicted value: 1,82 [mg/L] (equal to 5,54 [log(1/mol/L)])

WS warning: Water Solubility = 0,057 mg/L

Data gap filling method: Read-across analysis, Standardized workflow for (SW) Fish, LC50(EC50) at 96h for Pimephales promelas (mortality) (AW available)

Phthalate FR Analogues LC50 > solubility but LC50 < solubility * BCF

Analog name	CAS	Bioconcentration Factor (BCF)	ratio	Water	QSAR LC50 (fish)
		EpiSuite	LC50/solub.	solubility (mg/L)	mg/L
1-[2-(2-hydroxyethoxy)ethyl] 2-(2-hydroxypropyl) tetrabromophthalate	20566-35-2	86.2	32	0.057	1.82
Tetrabromophthalic acid dimethyl ester	55481-60-2	1298	145	0.0215	3.11
Diallyl tetrabromophthalate	49693-09-6	16960	42	0.000355	0.015

$$BCF = \frac{concentration\ in\ organism}{concentration\ in\ water}$$

Wrapping Up

- No tool was perfect – they are evolving!
- Each tool provided part of the story or confirmed/contradicted empirical information
- Board did not rely on any one tool
- Expert judgement is required!!!