

Incorporating exposure information into Toxicological Priority Index (ToxPI) for Chemical Prioritization

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY COMPUTATIONAL TOXICOLOGY

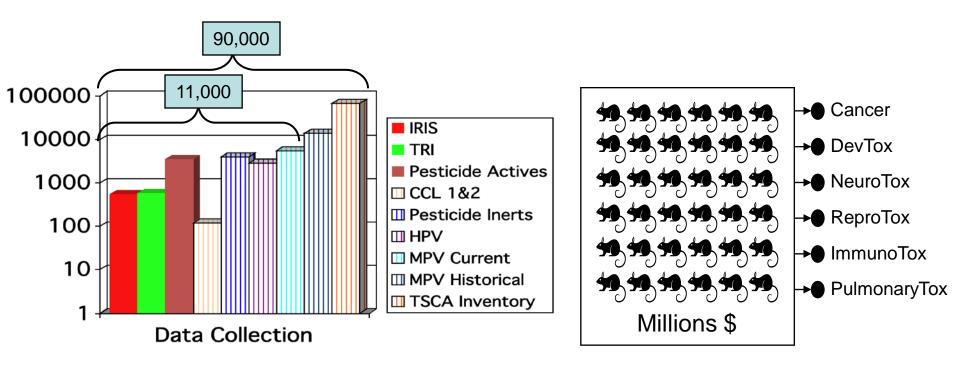
Office of Research and Development National Center for Computational Toxicology This work was reviewed by EPA and approved for presentation but does not necessarily reflect Agency policy



Traditional toxicology testing paradigm needs to change because . . .

Too Many Chemicals

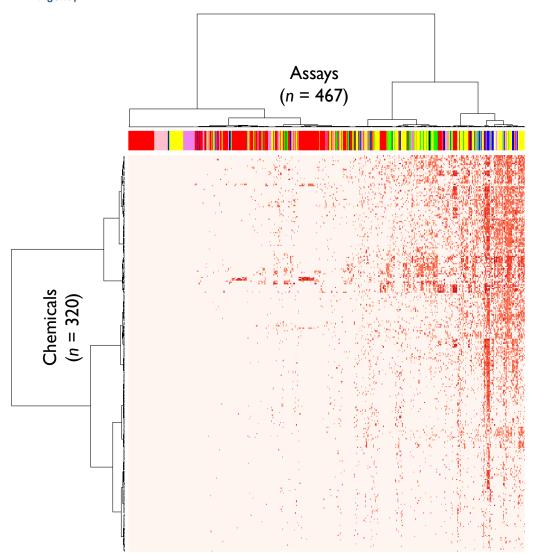
Too High a Cost



...and not enough data.



Diversity of data from ToxCast[™] in vitro HTS assays



Cellular Assays

- Cell lines
 - HepG2 human hepatoblastoma
 - A549 human lung carcinoma
 - HEK 293 human embryonic kidney

Primary cells

- Human endothelial cells
- Human monocytes
- Human keratinocytes
- Human fibroblasts
- Human proximal tubule kidney cells
- Human small airway epithelial cells

Biotransformation competent cells

- Primary rat hepatocytes
- Primary human hepatocytes

Assay formats

- Cytotoxicity
- Reporter gene
- Gene expression
- Biomarker production
- High-content imaging for cellular phenotype

Biochemical Assays

Protein families
 _ GPCR

NR

Kinase Phosphatase Protease Other enzyme Ion channel Transporter

- Assay formats
 - Radioligand binding
 - Enzyme activity
 - Co-activator recruitment

3

http://www.epa.gov/ncct/toxcast/

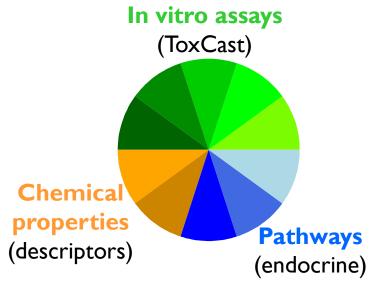
EPA CompTox Comm. of Practice 22 July 2010 Judson et al., 2010, Environ. Health Perspect. (doi: 10.1289/ehp.0901392)



Rationale for an integrated chemical prioritization scheme

- Integration over multiple domains of information
- Extensibility to incorporate additional types of data
- Transparency in score derivation and visualization
- Flexibility to customize components for diverse prioritization tasks





Putative endocrine profiles

 A numerical index that can be used for ranking (instead of absolute thresholds) is more flexible for different prioritization tasks.
 Can better accommodate new data, new chemicals, data adjustments, etc.



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 A numerical index that can be used for ranking (instead of absolute thresholds) is more flexible for different prioritization tasks.
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Reif et al., 2010, submitted



Definitions & notation

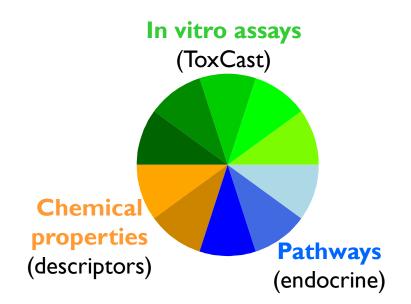
profile/ Each chemical signature/ gives a score index (ToxPi) used for ranking chemicals fingerprint

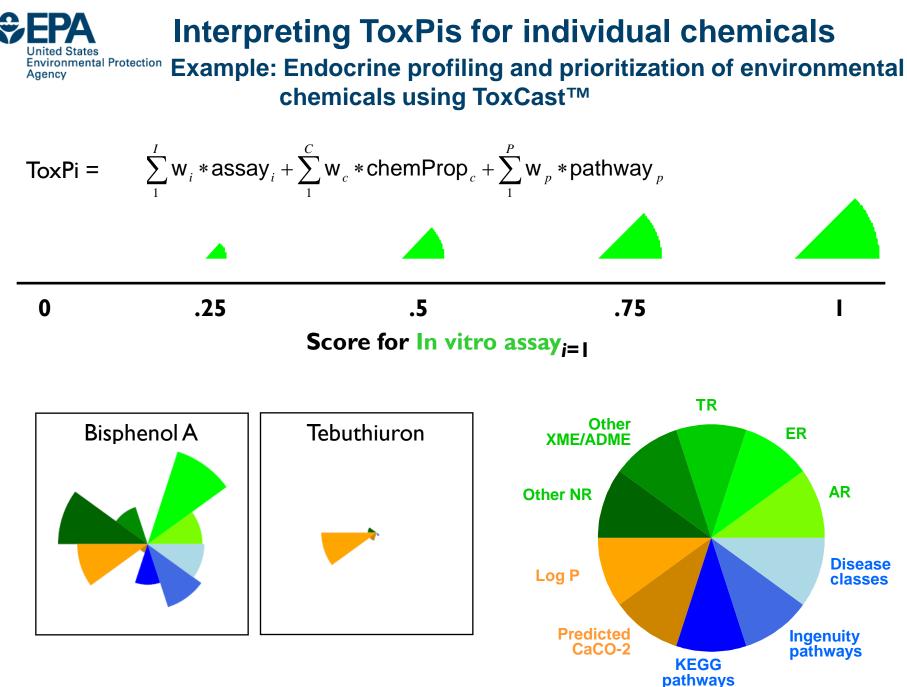
ToxPi = f(In vitro assays + Chemical properties + Pathways)

Domain: Domain/field of knowledge; represented by the slice(s) of a given color family

Slice: "Pie" slices representing individual components or aggregrations of multiple related components

Component: Individual in-vitro assays, chemical properties/descriptors, etc.

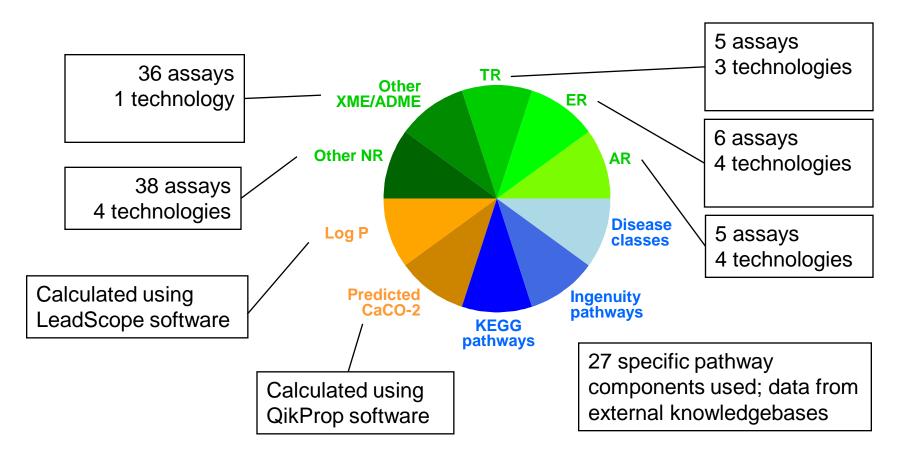


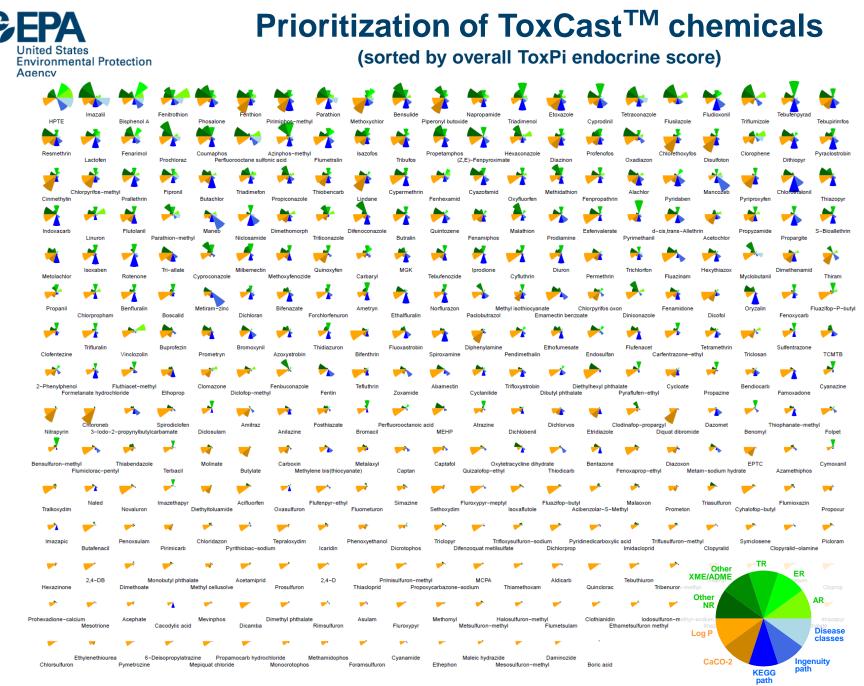


EPA CompTox Comm. of Practice 22 July 2010



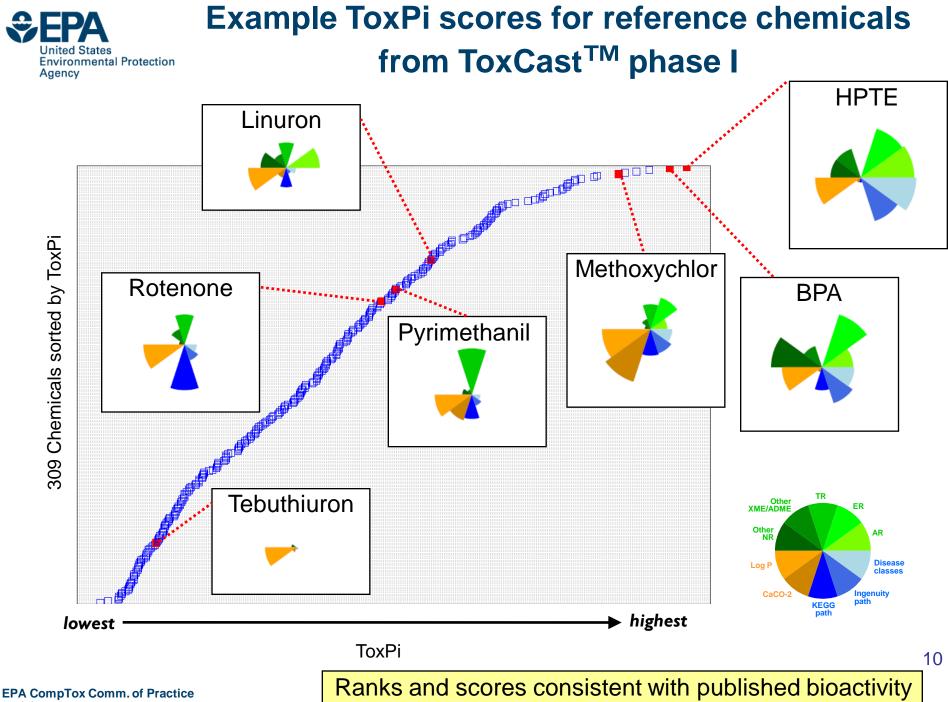
Example of data sources





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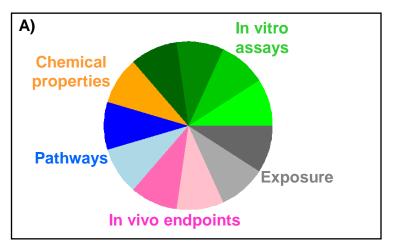
Reif et al., 2010, submitted



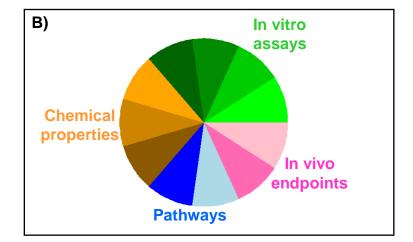
22 July 2010



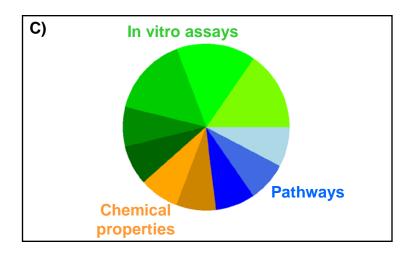
Alternative ToxPi implementations for different applications



A) Incorporate additional components (slices) from other domains



B) Customize individual domains (e.g. Add a targeted chemical descriptors)



C) Adjust weighting schemes (e.g. Weights of In vitro assay slices AR, ER, and TR have been increased)



Does typical info used to prioritize based on potential for exposure change ToxPi ranking?

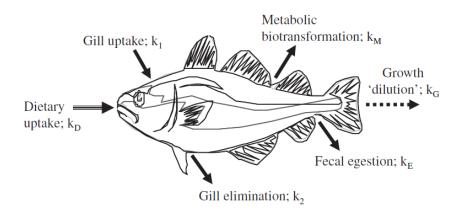
- Environmental fate parameters (bioaccumulation, persistence)
 - U.S. EPA: Identifies new/existing chemicals as persistent or bioaccumulative
 - \rightarrow Completing screening level risk assessment.
 - U.S. EPA. Category for Persistent, Bioaccumulative, and Toxic (PBT) New Chemical Substances. Federal Register, 1999, Vol. 64, pp 60194-60204.
 - Environment Canada: Identifies existing substances from Domestic Substances List that are persistent or bioaccumulative to non-human species.
 - Canadian Environmental Protection Act (CEPA), 1999
 http://www.ec.gc.ca/substances/ese/eng/dsl/cat_criteria_process.cfm

- Manufacturing production / use information
 - U.S. EPA's New Chemicals Program: Requires production volume info and use category for premanufacturing notice submission.
 - Health Canada ranked chemicals by quantity in commerce, # of submitters, and sum of expert ranked use codes \rightarrow Greatest potential for exposure.
 - "Exposure-based Prioritization Health Canada Experience under the Canadian Environmental Protection Act", Christine Norman, March 2010



Source for preliminary exposure data of environmental fate

- Exposure data obtained from EPI Suite[™] v4.00 (<u>http://www.epa.gov/oppt/exposure/pubs/episuite.htm</u>):
 - Bioaccumulation/bioconcentration factor (Log BCF, Log BAF) from BCFBAF program
 - Persistence (half life air, half life water, persistence time) from Level III fugacity model, BIOWIN, AOPWIN programs

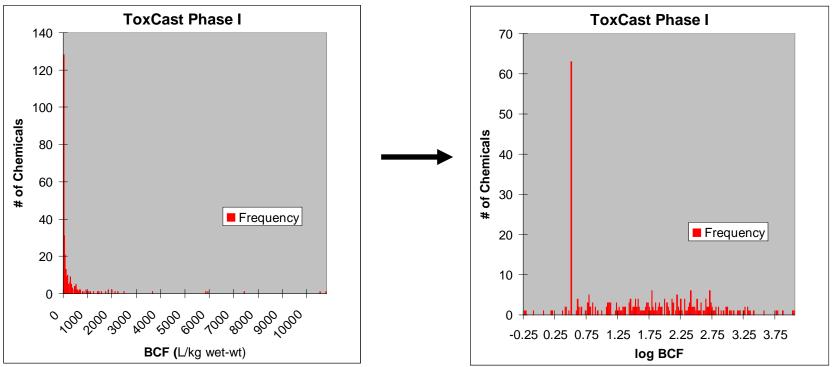


Arnot and Gobas, 2006, Environ. Rev.



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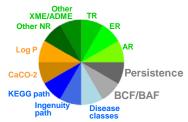
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 - Persistence (half life air, half life water, persistence time) from Level III fugacity model, BIOWIN, AOPWIN programs
- Ran EPI Suite[™] in batch mode passing chemicals smiles/CAS. From summary results, extracted data for 309 ToxCast Phase I chemicals
- Adjusted data range for negative values
- Normalized data to incorporate exposure domain into ToxPi framework with other data domains



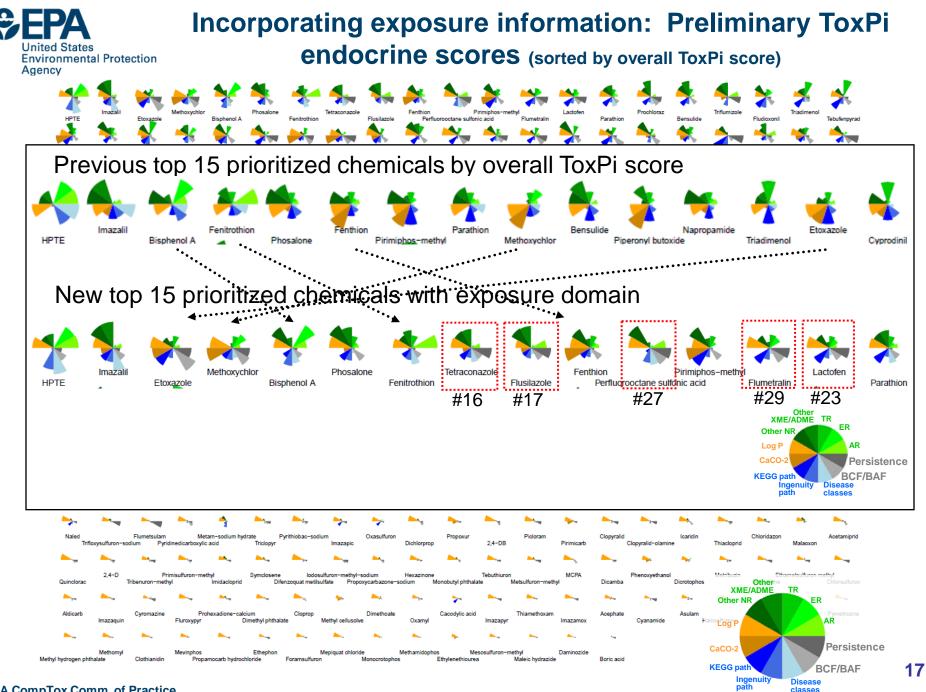


Incorporating exposure information: Preliminary ToxPi endocrine scores (sorted by overall ToxPi score)

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HPTE	Imazalil	Etoxazole	Methoxychlor	Bisphenol A	Phosalone	Fenitrothion	Tetraconazole	Flusilazole	Fenthion Perfluc	F prooctane sulfo	Pirimiphos-meth nic acid	Flumetralin	Lactofen	Parathion	Prochloraz	Bensulide	Triflumizole	Fludioxonil	Triadimenol	Tebufenpyrad
	*				*		**		X				X	*	*	*			4	Quintozene
Piperonyl butoxic	Napropamide	Cyprodinil	Fenarimol	Tebupirimfos	Dithiopyr	Chlorethoxyfos	Lindane	Resmethrin	Coumaphos	Cypermethrin	Fipronil	Oxyfluorfen (Z	,E)-Fenpyroxim	Pyraclostrobin ate	Oxadiazon	Isazofos	Chlorothalonil	Hexaconazole	Profenofos	Quintozene
	Puridaban	* **		₩.	Cinmethylin	→	Propetamphos)	Clorophene	*	Buring under	-	Disulfoton		Butachlor	*	Triadimefon		Fenpropathrin	*
Azinphos-methy	Pyridaben yl	Indoxacarb	Dienoconazole	Tribufos	Cinnediyiin	Thiazopyr	Ch	lorpyrifos-met	nyl	Diazinon	Pyriproxyfen	Propiconazole		Quinoxyfen	Dutachion	Esfenvalerate	madimeton	Fenhexamid	renpropaulini	Prodiamine
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Emamectin benzo	Thiobencarb	Cyfluthrin	Fluazinam	Dicofol	Cyazofamid	Niclosamide	Alachlor	Prallethrin	Butralin	Milbemectin	Linuron	Propargite	Benfluralin	Flutolanil	Bifenthrin	Triticonazole	Ethalfluralin	Tri-allate	Trifluralin	Propyzamide
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Tefluthrin	Dichloran	Malathion	Flufenacet	Propanil	Maneb	Trifloxystrobin	Zoxamide	Bifenazate Ca	arfentrazone-et	lprodione hyl	Abamectin	MGK	Carbaryl	Myclobutanil F	luazifop-P-but	Paclobutrazol yl	Clofentezine	Spiroxamine	Chlorpropham	Spirodiclofen
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Methyl hydrogen phti	Methomyl halate	Clothianidin	Mevinphos Propa	mocarb hydroc	Ethephon	N Foramsulfuron	lepiquat chlorid	e Monocrotophos	Methamidophos	s M Ethylenethioure	esosulfuron-me a	thyl Maleic hydrazid	Daminozide le	Boric acid			CaCO-2			Persiste
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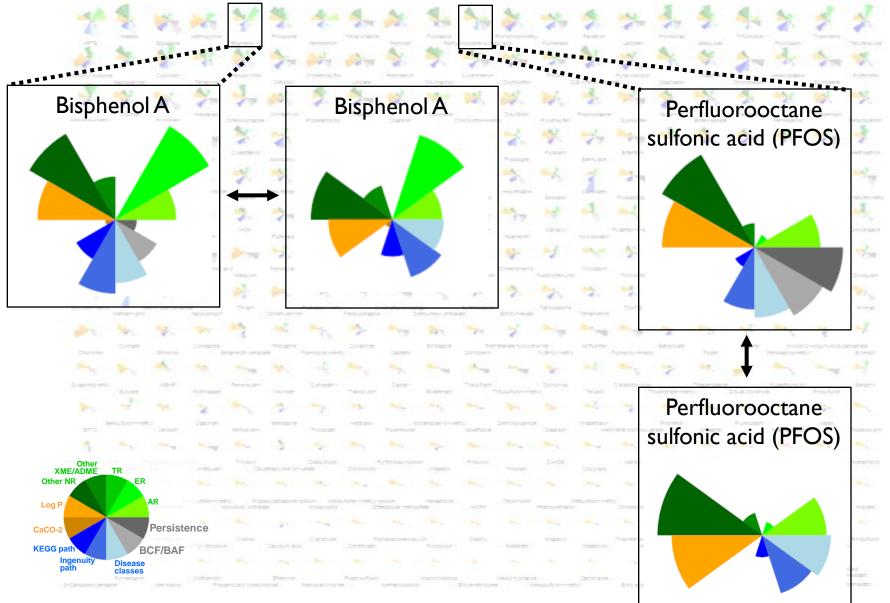
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Interpreting ToxPis with exposure domain for individual chemicals



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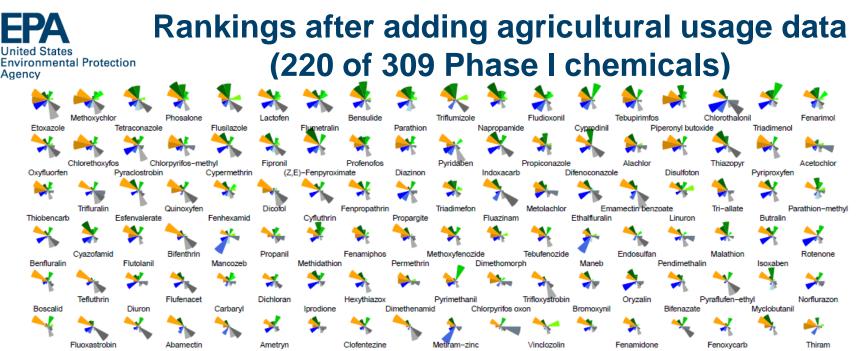
Agency

Environmental Protection



Pesticide agricultural usage data

- Data provider is GfK Kynetec, a private market research firm. Proprietary database is called Agro Trak. Based on surveys of pesticide use on over 50 agricultural crops.
- Data provides an estimate of the pounds of each active ingredient (AI) applied to agricultural crops on a national level. Does not include Non-Ag. data (home and garden use, turf and ornamentals, etc.).
 - → Data available for 220 of 309 ToxCast Phase 1 chemicals for which agricultural pesticide usage was reported.
 - Reported pounds of AI applied per year (from 1998 to 2008) was summed over the 11 years and then normalized.



Fluazifop-P-butyl Carfentrazone-ethyl Prometryn Spirodiclofen Cyanazine Buprofezin Zoxamide Atrazine Azoxystrobin -

Ethoprop Thidiazuron Propazine Flumiclorac-pentyl Sulfentrazone Fenbuconazole Clomazone Novaluron Cyclanilide Clodinafop-propargyl Fluthiacet-methyl Famoxadone Chloroneb Acifluorfen Diclosulam Ethofumesate Cycloate Amitraz ∽_

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Thiophanate-methyl Bromacil Dichlobenil Butylate Penoxsulam Fluometuron Diquat dibromide Sethoxydim Captan Molinate Quizalofop-ethyl Formetanate hydrochloride Fenoxaprop-ethyl Bentazone Fluazifop-butyl Tralkoxydim Triasulfuron Simazine

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2.4-D Imazethapyr Acibenzolar-S-Methyl Cymoxanil Terbacil Bensulfuron-methyl Metalaxvl Dazomet Flumioxazin Cyhalofop-butyl Benomyl Triflusulfuron-methyl Prosulfuron Thiodicarb Isoxaflutole Carboxin Triclopyr Oxytetracycline dihydrate

Prometon Naled Clopyralid-olamine Pyrithiobac-sodium Dicamba Imazapic Quinclorac Imidacloprid Metribuzin Flumetsulam Picloram Clopyralid 2.4-DB Trifloxysulfuron-sodium MCPA Aldicarb Dichlorprop Chloridazon

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Acetamiprid Thiacloprid Pirimicarb Difenzoguat metilsulfate Dimethoate Tebuthiuron Metsulfuron-methyl Mesotrione Fluroxypyr Hexazinone Dicrotophos Primisulfuron-methyl Tribenuron-methyl Acephate Ethephon Propoxycarbazone-sodium Oxamvl Imazaguin Othe

Methomyl Chlorsulfuron Cvanamide Cyromazine Clothianidin Imazapyr Halosulfuron-methyl Propan Asulam lodosulfuron-methyl-sodium Thiamethoxam Imazamox Ethametsulfuron methyl Prohexadione-calcium Rimsulfuron Mepiquat chloride l og

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Foramsulfuron Mesosulfuron-methyl Methamidophos Mevinphos

Agency

Persistence BCF/BAF 20

Ag usage

XME/ADME

Disease

classes

Other NR

CaCO-2

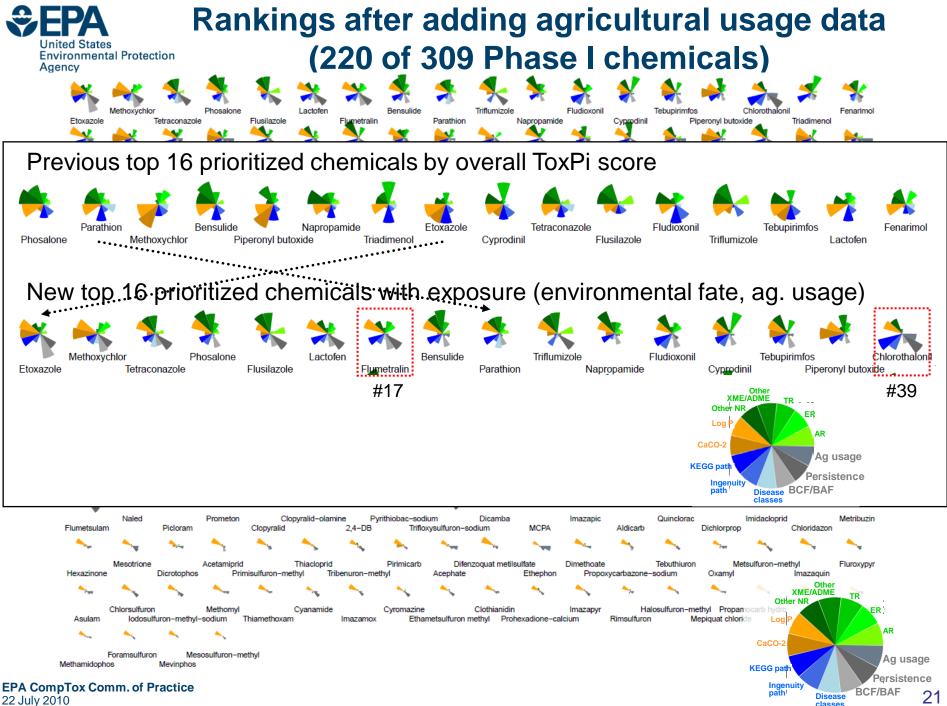
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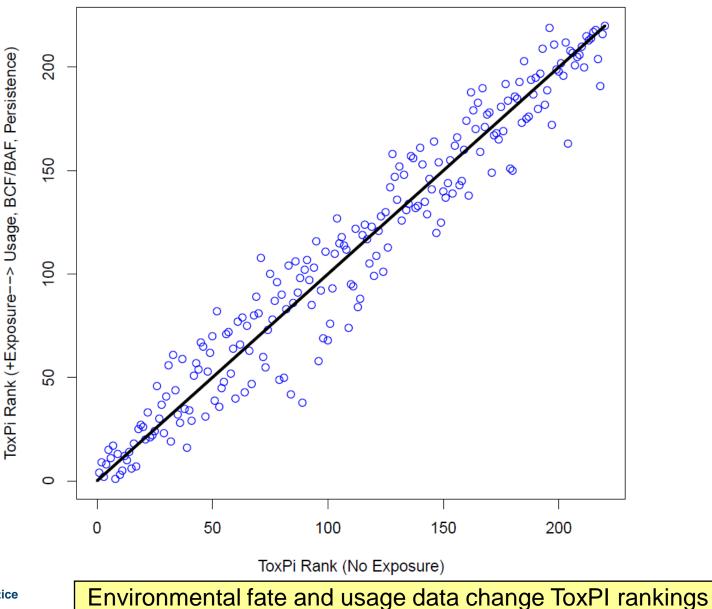
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AR



Change in ToxPI ranking after adding agricultural usage data (220 chemicals)





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Limitations of environmental fate parameters

- Bioaccumulation in humans \rightarrow NOT studied
 - Humans at top of both aquatic and terrestrial food chains → Evidence suggests bioaccumulation based on aquatic food chains only may not be appropriate for humans.

Czub and McLachlan, 2004, Environ. Sci. Technol.

- Uncertainty in BCF and BAF values can be high (up to a factor of ~3 for BAF). Arnot and Gobas, 2006, *Environ. Rev.*
- Decisions for screening assessments by setting cutoffs for BCF and persistence can be flawed.
 - Proposed holistic method integrating persistence, bioaccumulation, toxicity (PBT) and quantity.

Arnot and Mackay, 2008, Environ. Sci. Technol.



Do fate parameters prioritize chemicals detected during residential exposure?

- Humans spend much of their time indoors.
 - Exposure to semivolatile organic compounds (SVOCs) indoors contribute to detectable body burdens (CDC's National Report on Human Exposure to Environmental Chemicals)

Weschler and Nazaroff, 2008, Atm. Environ. ; Weschler and Nazaroff, 2010, submitted

- For example, phthalates are detected not only in consumer products \rightarrow Also in food and in indoor environment (air and household dust).
 - But, exposure to phthalates does not result in bioaccumulation (based on chemical properties).

Heudorf et al., 2007, Int. J. Hyg. Environ. Health



Endocrine disrupting compounds in indoor air and dust

CHEMICAL CLASS

(IN ORDER OF ABUNDANCE IN DUST)

SOURCES

Phthalates	Plastics, adhesives, personal care products, and other sources
Alkylphenols	Surfactants in cleaners, inerts in pesticides, personal care products, plastics, and other sources
Pesticides, pesticide metabolites	Pesticides
Polycyclic aromatic hydrocarbons (PAHs)	Products of combustion
Parabens	Personal care products and other sources
Phenolics (e.g., bisphenol A)	Plastics, personal care products, and other sources
Miscellaneous (e.g., dichlorophenol, nitrophenol)	Miscellaneous household products
Polychlorinated biphenyls (PCBs)	Electrical equipment

- Analyzed 89 compounds compounds found in indoor air and house dust samples from 120 homes in Cape Cod, MA.
 - Eligible women either breast cancer cases or age-matched controls. Lived in their homes at least 10 years.
- Criteria for compounds selection
 - Evidence that they were EDCs
 - Reported to be in commercial products or building materials
 - Compatible with one of two GC/MS analytical methods for detection

Rudel et al., 2003, Environ. Sci. & Tech.



EDC compounds detected in indoor air and dust

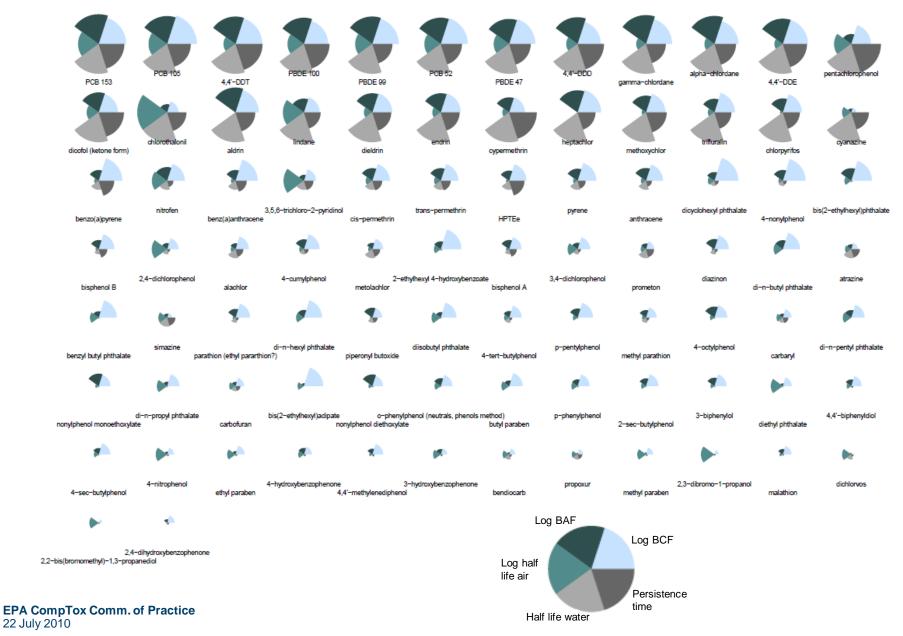
• Of 89 compounds analyzed in 120 homes:

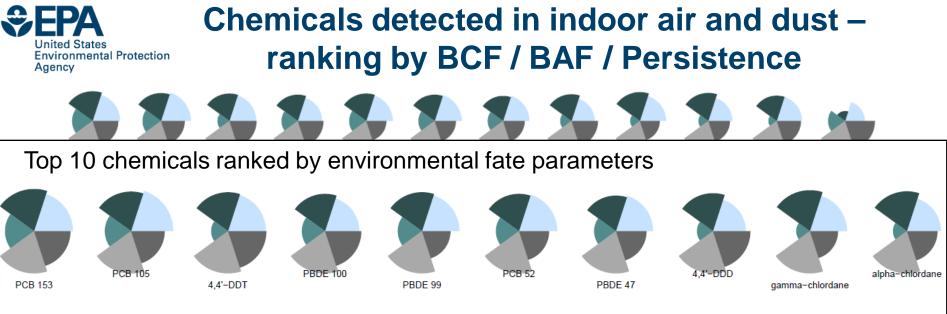
Indoor Air	Household dust
 52 compounds detected 23 pesticides 	 66 compounds detected 27 pesticides
 13 to 28 compounds per home 	 6 to 42 compounds per home
 Most abundant chemicals include: phthalates (plasticizers, emulsifiers), o-phenylphenol (disinfectant), 4- nonylphenol (detergent metabolite) and 4-tert-butylphenol (adhesive) Typical concentrations in range of 50-1500 ng/m³ 	• Penta- and tetrabrominated diphenyl ethers (flame retardants) frequently detected in dust; Most abundant pesticides include permethrins and synergist piperonyl butoxide

• 2,3-dibromo-1-propanol (carcinogenic intermediate of a flame retardant banned in 1977) detected in both air and dust

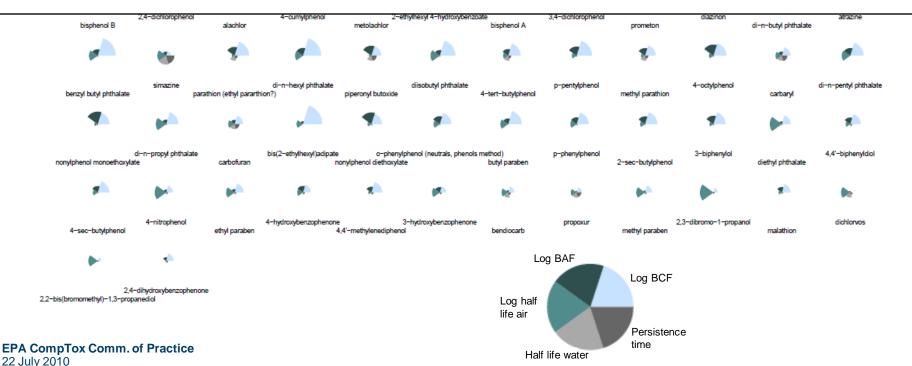


Chemicals detected in indoor air and dust – ranking by BCF / BAF / Persistence





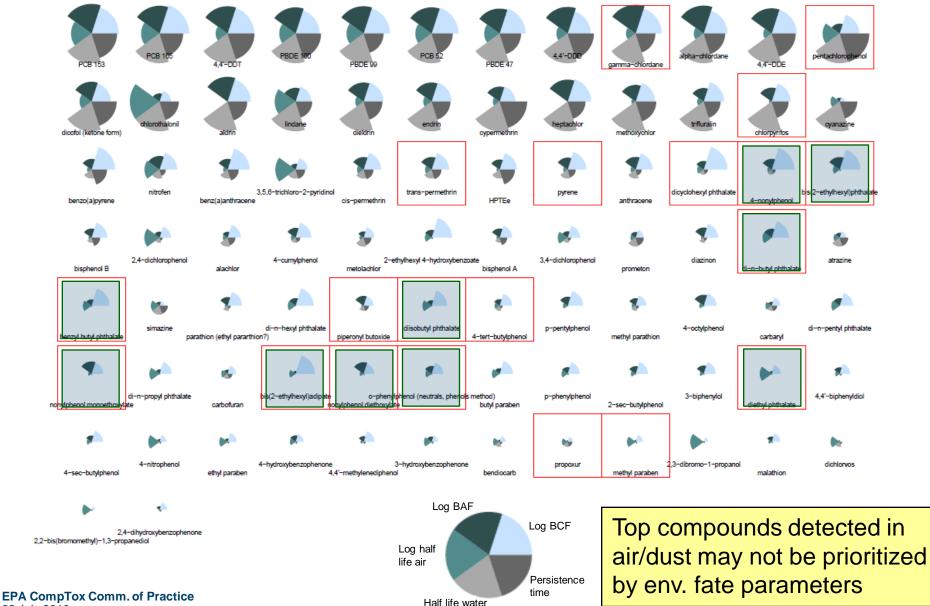
... How does this ranking compare to what is <u>detected in air and dust</u>?





Chemicals detected in indoor air and dust

(top 20 concentrations highlighted by red boxes; top 10 conc. shaded)



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Indoor air and dust chemicals—Overlap with ToxCast Phase I chemicals

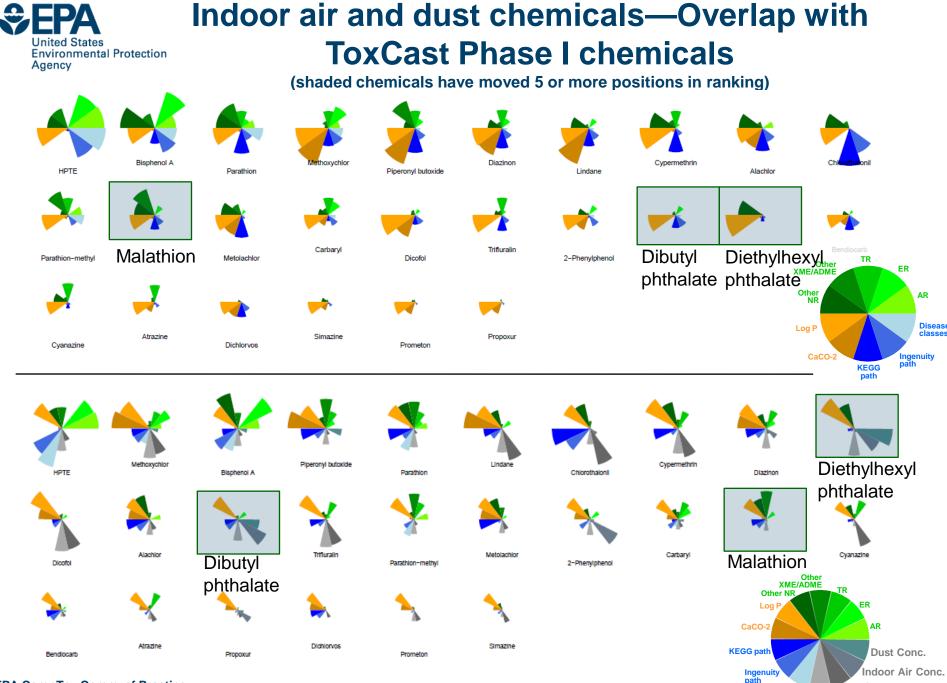


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United States

Agency

Environmental Protection



Disease

classes

Persistence

BCF/BAF

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Conclusions

- ToxPi profiles provide <u>transparent visualization</u> of relative contribution of all info sources to an overall priority ranking.

Toxicological data components selected based on putative endocrine relevance.
 → Method developed readily adaptable to diverse chemical prioritization tasks.

- Adding exposure domain changes ToxPi scores for ToxCast compounds.

- Environmental fate parameters may not prioritize key chemicals to which humans are exposed to indoors

- Future plans:

- Incorporate other exposure metrics (manufacturing volumes, non-agricultural usage, measured data in food, biomonitoring data, etc.) into ToxPi analysis.

- Perform value of information analysis. Weight slices differently or remove slices.



Acknowledgments

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Elaine Cohen Hubal David Reif Tom Transue ToxCast Project – Keith Houck, Richard Judson, Ann Richard... David Dix Robert Kavlock

EPA National Exposure Research Laboratory (NERL), Office of Research and Development

Peter Egeghy

EPA Office of Pesticide Prevention (OPP), Office of Chemical Safety and Pollution Prevention

Katherine Stebbins

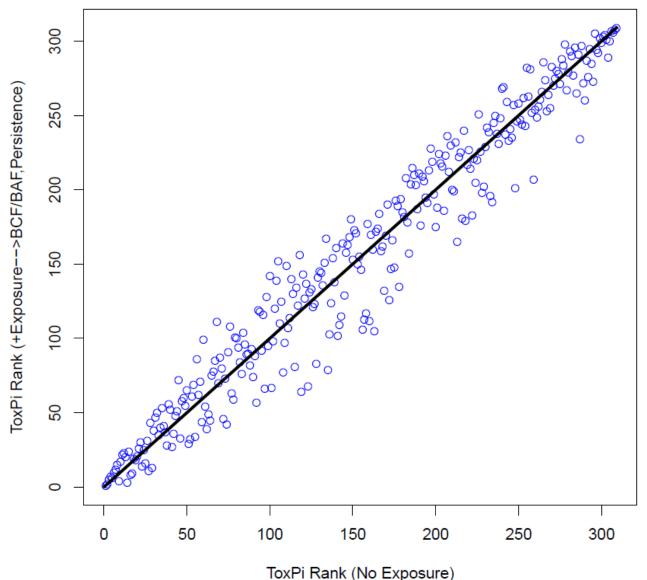
Silent Spring Institute, Newton MA Ruthann Rudel Robin Dodson

... plus many more EPA colleagues that are participating in the continued development of this project

This work was reviewed by EPA and approved for presentation but does not necessarily reflect Agency policy

Change in ToxPI ranking after adding environmental fate metrics

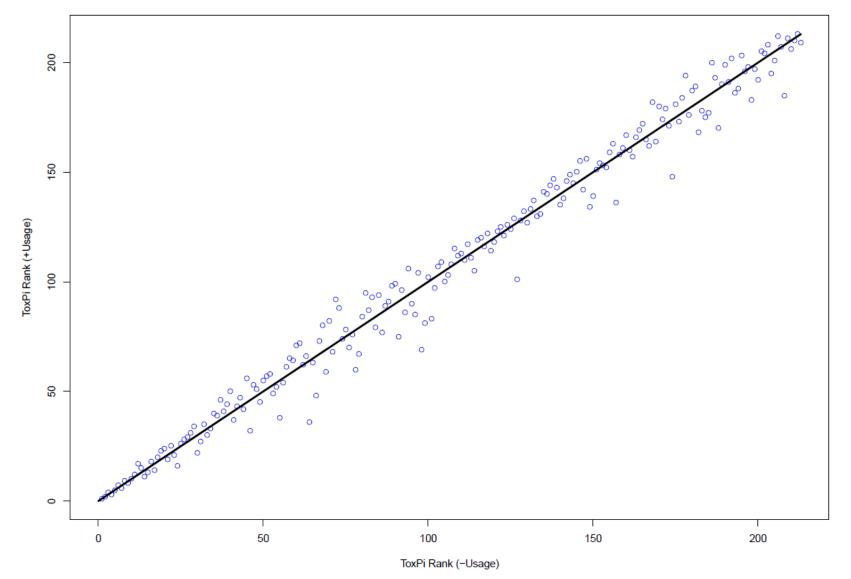




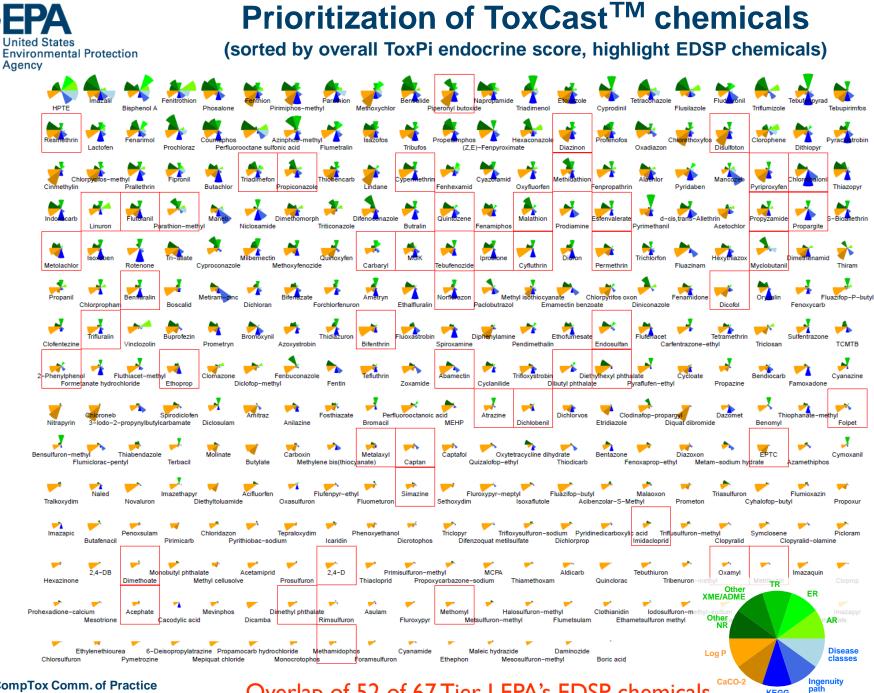
EPA CompTox Comm. of Practice 22 July 2010



Change in ToxPI ranking after adding agricultural usage data (subset of 309 chemicals)



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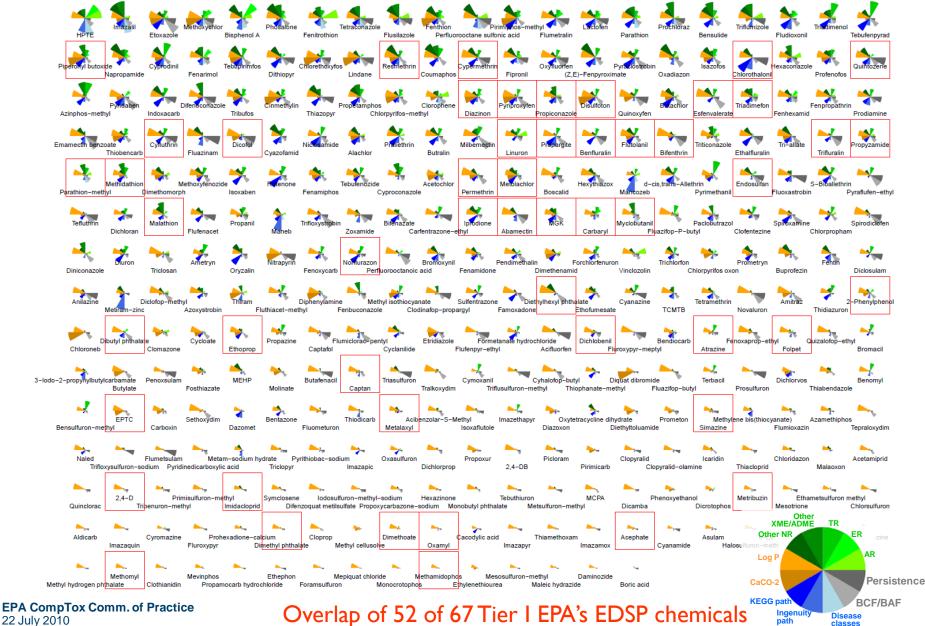
Overlap of 52 of 67 Tier I EPA's EDSP chemicals

KEGG

path



Incorporating exposure information: Preliminary ToxPi endocrine scores (sorted by overall ToxPi score, highlight EDSP chemicals)

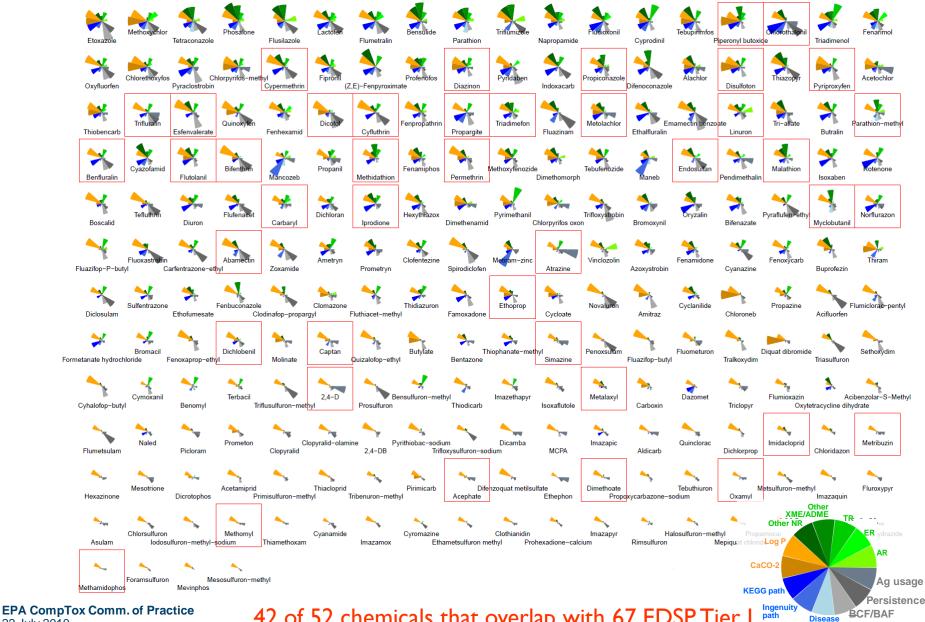


22 July 2010



Rankings after adding usage slice

(highlight EDSP chemicals)



²² July 2010

42 of 52 chemicals that overlap with 67 EDSP Tier I

classes

United States Environmenta Agency	al Protection	End	ocrine	e dis	rupti	ng co and o		ound	s in ir	ndoo	or air
									•	•	•
lis(2-ethylhexyl)phthalate	benzyl butyl phthalate	di-n-butyl phthalate	diethyl phthalate	4-nonyiphenol	diisobutyl phthalate o-phenyl	bis phenol (neutrals,phenols r	(2-ethylhexyl)adipate method) non	ylphenol monoethoxy	nonylphenol diethoxylate late	methyl paraben	propoxur
	•	•	•	•			•		•		-
4-tert-butylphenol	pentachlorophenol	chlorpyrifos	dicyclohexyl phthalate g	amma-chlordane	trans-permethrin	piperonyl butoxide	pyrene	heptachlor	alpha-chlordane	diazinon	cis-permethrin
•	•	•	-	-	٠	-	÷	-	•	-	٠
di-n-hexyl phthalate	4,4'-DDT	chlorothalonil	PBDE 99	bisphenol A	carbaryl	benzo(a)pyrene	4-nitrophenol	methoxychlor	di-n-propyl phthalate 2,4-	3 dihydroxybenzophen	3,5,6-trichloro-2-pyridinol one
	•	•	-	-	-		*	•	•	*	
PCB 52	benz(a)anthracene	PBDE 47	2,4-dichlorophenol	bendiocarb	PBDE 100	trifluralin	PCB 153	anthracene	butyl paraben	dieldrin	4,4'-DDE
2,3-dibromo-1-propanol	cypermethrin	lindane	methyl parathion	PCB 105	ethyl paraben	4,4'-methylenediphenol	prometon	4,4'-DDD	4,4'-biphenyldiol	p-phenylphenol	dicofol (ketone form)
malathion	4-cumylphenol	alachlor	3-biphenylol	4-octylphenol	di-n-pentyl phthalate	aldrin	atrazine	carbofuran	cyanazine	dichlorvos	endrin
HPTE	metolachlor	p nitrofen	arathion (ethyl pararthion?)	2,2-bis simazine	(bromomethyl)-1,3-pro 2-et	panediol thylhexyl 4-hydroxybenzoa	2-sec-butylphenol ate 3-	-hydroxybenzophenor	4-hydroxybenzophenone ne	4-sec-butylphenol	bisphenol B
										Air concentratio	on
p-pentylphenol	3,4-dichlorophenol								(

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Based on data from Rudel et al., 2003, Environ. Sci. & Tech.

Dust concentration