



The CompTox Dashboard & Emerging Contaminants in the Superfund Program

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US EPA Office of Land and Emergency Management (Superfund)

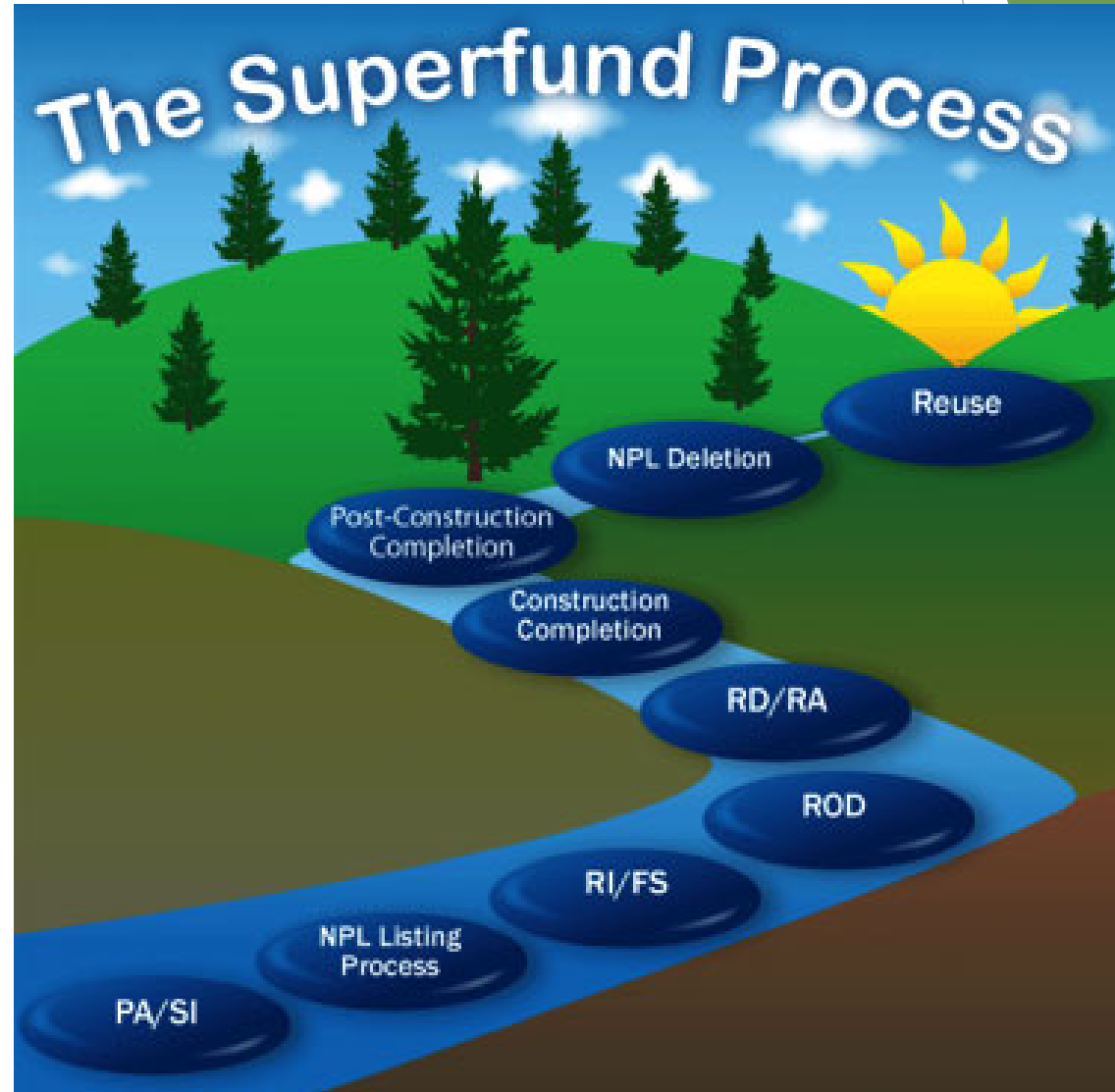
US EPA Office of Research and Development

August 20, 2017

The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA.

Background

- ▶ Superfund is an EPA program to clean up the most polluted sites in America that no other environmental program can successfully address
 - ▶ Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA) and SARA (1986)
 - ▶ Sites are evaluated for risks to human health or the environment
 - ▶ Currently 1336 NPL sites + 393 deleted sites
 - ▶ Sites may take years to address



42 U.S. Code § 9604 - Response authorities



(a)REMOVAL AND OTHER REMEDIAL ACTION BY PRESIDENT; APPLICABILITY OF NATIONAL CONTINGENCY PLAN; RESPONSE BY POTENTIALLY RESPONSIBLE PARTIES; PUBLIC HEALTH THREATS; LIMITATIONS ON RESPONSE; EXCEPTION

(1)Whenever (A) any hazardous substance is released or there is a substantial threat of such a release into the environment, or (B) there is a release or substantial threat of release into the environment of any pollutant or contaminant which may present an imminent and substantial danger to the public health or welfare, the President is authorized to act, consistent with the national contingency plan, to remove or arrange for the removal of, and provide for remedial action relating to such hazardous substance, pollutant, or contaminant at any time (including its removal from any contaminated natural resource), or take any other response measure consistent with the national contingency plan which the President deems necessary to protect the public health or welfare or the environment.



42 U.S. Code § 9604 - Response authorities

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42 U.S. Code § 9601 - Definitions

The term “**hazardous substance**” means (A) any substance designated pursuant to section 311(b)(2)(A) of the **Federal Water Pollution Control Act** [33 U.S.C. 1321(b)(2)(A)], (B) any element, compound, mixture, solution, or substance designated pursuant to section 9602 of this title, (C) any hazardous waste having the characteristics identified under or listed pursuant to section 3001 of the **Solid Waste Disposal Act** [42 U.S.C. 6921] (but not including any waste the regulation of which under the Solid Waste Disposal Act [42 U.S.C. 6901 et seq.] has been suspended by Act of Congress), (D) any toxic pollutant listed under section 307(a) of the **Federal Water Pollution Control Act** [33 U.S.C. 1317(a)], (E) any hazardous air pollutant listed under section 112 of the **Clean Air Act** [42 U.S.C. 7412], and (F) any imminently hazardous chemical substance or mixture with respect to which the Administrator has taken action pursuant to section 7 of the **Toxic Substances Control Act** [15 U.S.C. 2606].




42 U.S. Code § 9601 - Definitions

The term “**pollutant or contaminant**” shall include, but not be limited to, any element, substance, compound, or mixture, including disease-causing agents, which after release into the environment and upon exposure, ingestion, inhalation, or assimilation into any organism, either directly from the environment or indirectly by ingestion through food chains, **will or may reasonably be anticipated to cause death, disease, behavioral abnormalities, cancer, genetic mutation, physiological malfunctions (including malfunctions in reproduction) or physical deformations**, in such organisms or their offspring ...



Data Sources for Pollutants and Contaminants

- ▶ Primary data sources:
 1. Integrated Risk Information System (IRIS) Assessments
 2. Provisional Peer Review Toxicity Values (PPRTVs)
 3. Other - other federal, state, international values, published studies
- ▶ Translate Point-of-Departure (POD) data to Reference Doses (RfDs)
- ▶ Risk Assessment Guidance for Superfund (RAGS) provides equations to translate toxicity and exposure into risks to human health



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
SOLID WASTE AND EMERGENCY
RESPONSE

December 5, 2003

OSWER Directive 9285.7-53

MEMORANDUM

SUBJECT: Human Health Toxicity Values in Superfund Risk Assessments

FROM: Michael B. Cook, Director /s/
Office of Superfund Remediation and Technology Innovation


TO: Superfund National Policy Managers, Regions 1 - 10

Purpose

This memorandum revises the hierarchy of human health toxicity values generally recommended for use in risk assessments, originally presented in Risk Assessment Guidance for Superfund Volume I, Part A, Human Health Evaluation Manual (RAGS) (OSWER 9285.7-02B, EPA/540/1-89/009, December 1989).
<http://www.epa.gov/superfund/programs/risk/ragsa/index.htm>

It updates the hierarchy of human health toxicity values and provides guidance for the sources of toxicity information that should generally be used in performing human health risk assessments at Comprehensive Environmental Response Compensation and Liability Act (CERCLA or "Superfund") sites. It does not address the situation where new toxicity information is brought to the attention of the U.S. Environmental Protection Agency (EPA). It also does not provide guidance or address toxicity or reference values for ecological risk.

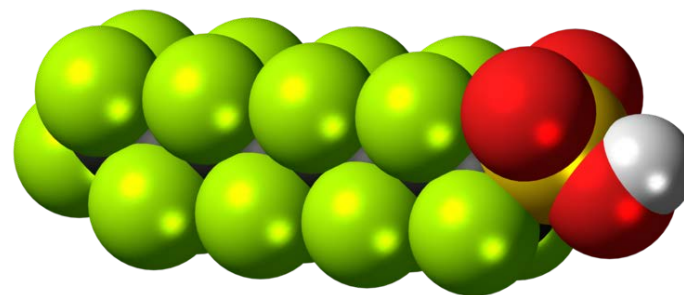
This memorandum presents current Office of Solid Waste and Emergency Response (OSWER) technical and policy recommendations regarding human health toxicity values in risk assessments. EPA and state personnel may use and accept other technically sound approaches, either on their own initiative, or at the suggestion of potentially responsible parties, or other interested parties. Therefore, interested parties are free to raise questions and objections about the substance of this memorandum and the appropriateness of the application of this document to a particular situation. EPA will, and States should, consider whether the recommendations or interpretations in this memorandum are appropriate in that situation. This memorandum does not impose any requirements or obligations on EPA, States, or other federal agencies, or the regulated community. The sources of authority and requirements in this matter are the relevant


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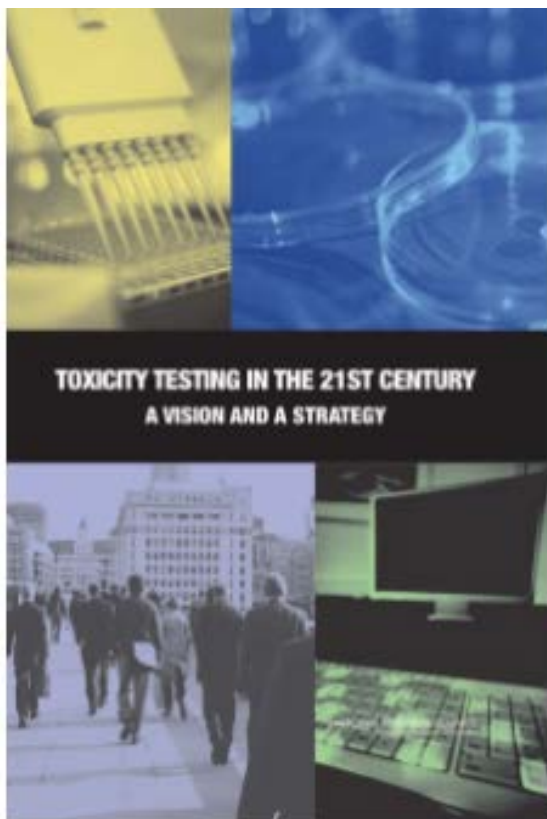


Emerging Contaminants

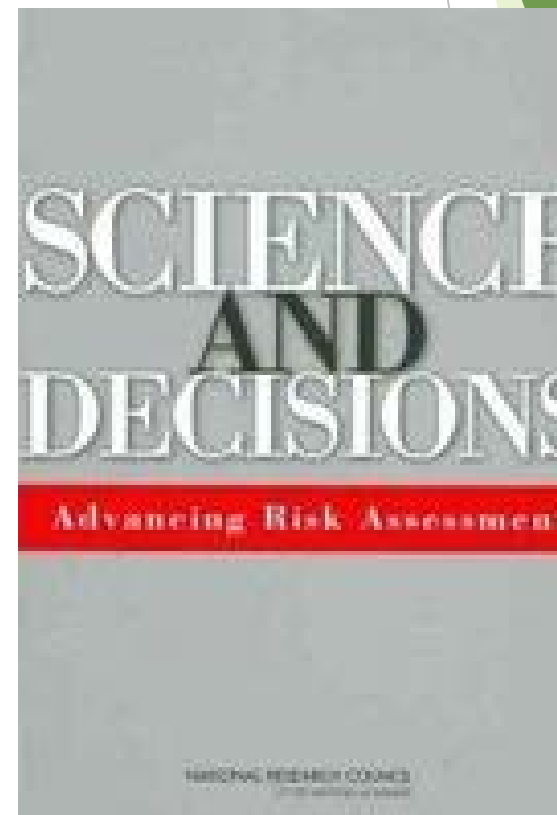
- ▶ New chemicals of concern with limited, or no, toxicity data
 - ▶ Perfluorinated compounds
 - ▶ Brominated flame retardants
 - ▶ Endocrine disruptors
 - ▶ Nanomaterials
- ▶ Current approach:
 - ▶ Hazardous substance designation
 - ▶ Wait for a PPRTV or IRIS assessment



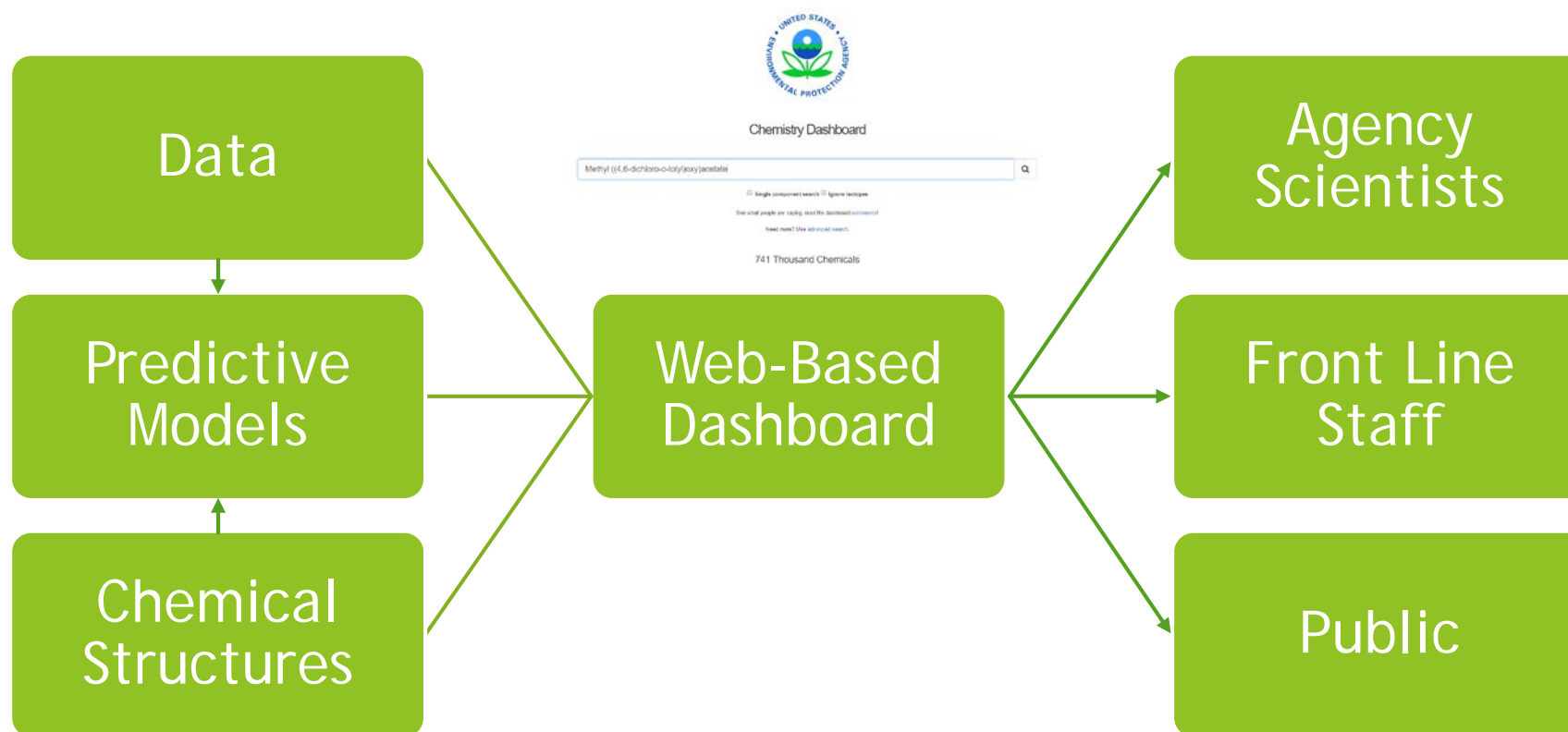
Motivation



- ▶ 2007 NAS Report: Toxicity Testing in the 21st Century
- ▶ Need to incorporate in vitro data, predictive models in risk assessments
- ▶ CompTox dashboard:
 - ▶ One-stop-shop for existing data
 - ▶ Easy to use tools to predict toxicity, physical properties



CompTox Dashboard



Current Public Dashboard: <https://comptox.epa.gov/>



Why CompTox?

- ▶ Coverage for information poor chemicals
- ▶ Single point of entry to data
 - ▶ Structure
 - ▶ Physical properties
 - ▶ Toxicity
 - ▶ Exposure
 - ▶ Regulatory data
- ▶ Access to robust, transparent, and defensible predictive models

PFOA
335-67-1 | DTXSID8031865 **~760,000 chemicals**
>15 years of data

Searched by Approved Name: Found 1 result for 'PFOA'.

Wikipedia
Perfluorooctanoic acid (PFOA) (conj)

Intrinsic Properties
Structural Identifiers
Related Compounds
Presence in Lists
Record Information

Executive Summary | Chemical Properties | Env. Fate/Transport | Toxicity Values (Beta) | ADME (Beta) | Exposure

Summary

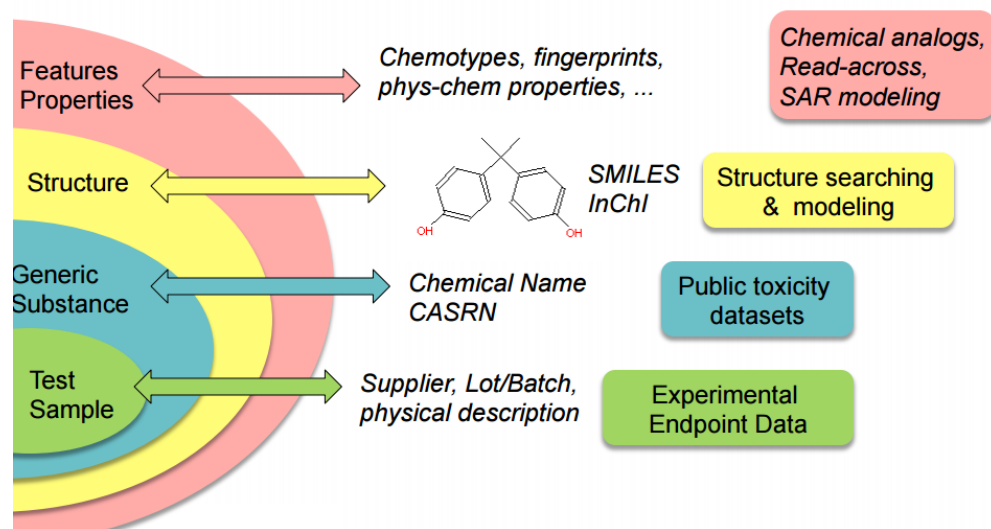
LogP: Octanol-Water
Water Solubility
Density
Flash Point
Melting Point
Boiling Point
Surface Tension

Download as: TSV | Excel | SDF

Property	Average	
	Experimental	Predicted
LogP: Octanol-Water	-	5.68 (5)
Water Solubility	-	2.84e-01 (3)
Density	-	1.75 (1)
Flash Point	-	62.1 (1)
Melting Point	57.4 (12)	48.7 (3)
Boiling Point	189 (7)	192 (4)
Surface Tension	-	16.8 (1)
Vapor Pressure	5.25e-01 (1)	1.83e-01 (3)



Chemical Structures



- ▶ Chemical structures are essential:
 - ▶ How we identify unique chemicals
 - ▶ Used as inputs for predictive modelling
 - ▶ Often used to define regulatory and use classes
- ▶ Manually curated by chemists
- ▶ Currently integrating chemical mixtures
 - ▶ Some mixtures have fixed ratios
 - ▶ Some have variable or unknown ratios
 - ▶ Different frameworks for understanding mixture toxicity
 - ▶ Tackling how models can incorporate mixtures



Curated Data

► Toxicity data

► In Vivo Chemical Toxicity Data:

- Risk assessments for chemical registrations
- EPA chemical evaluations
- Literature
- Publically available databases

► In Vitro Toxicity Data - ToxCast

► Exposure: NHANES

► Regulatory data

- State, Federal, International
- Exposure limits, regulatory classes

Organized into an ontology

Data must be:

- Quality controlled
- Associated with chemical structures and unique sources
- Assigned a hierarchy score

Displayed as raw data in dashboard
Used as inputs for predictive models
Combined for risk assessments



Predictive Models

- ▶ Physical properties:
 - ▶ EPISUITE
 - ▶ NICEATM
 - ▶ ACD/Labs
 - ▶ T.E.S.T.
 - ▶ OPERA
- ▶ ADME properties - used for *in vivo in vitro* extrapolation
- ▶ Toxicity
 - ▶ Generalized read-across (GenRA)
 - ▶ Point-of-Departure predictions
- ▶ Exposure
 - ▶ Use categories
 - ▶ Far field exposure

Physical Properties



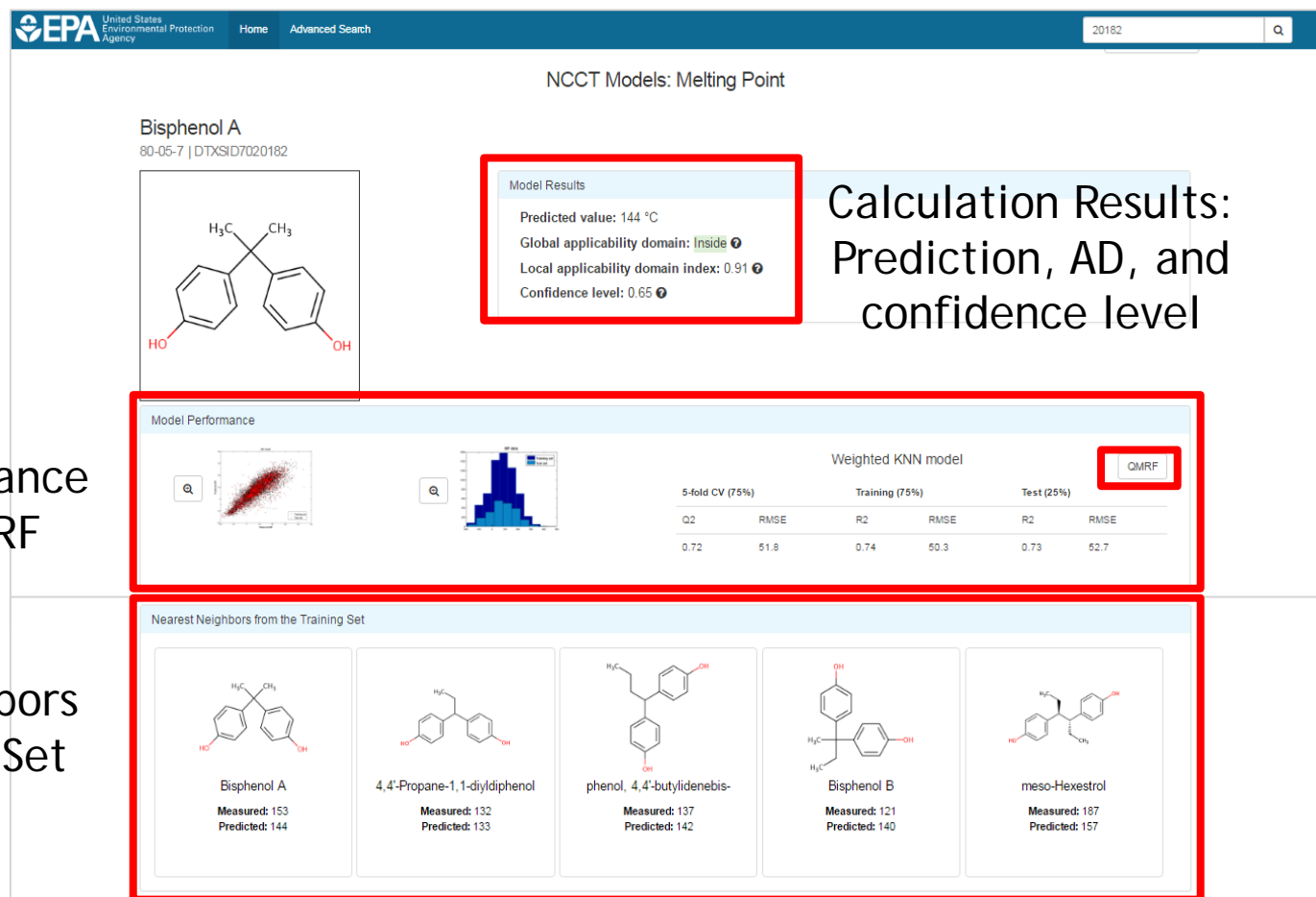
Summary
LogP: Octanol-Water
Water Solubility
Density
Melting Point
Boiling Point
Surface Tension
Vapor Pressure
LogKoa: Octanol-Air
Henry's Law
Index of Refraction
Molar Refractivity
pKa Acidic Apparent

Download as: TSV Excel SDF

Property		
LogP: Octanol-Water	<input checked="" type="checkbox"/>	Select/Deselect All
Water Solubility	<input checked="" type="checkbox"/>	LogP: Octanol-Water
Density	<input checked="" type="checkbox"/>	Water Solubility
Melting Point	<input checked="" type="checkbox"/>	Density
Boiling Point	<input checked="" type="checkbox"/>	Melting Point
Surface Tension	<input checked="" type="checkbox"/>	Boiling Point
Vapor Pressure	<input checked="" type="checkbox"/>	Surface Tension
LogKoa: Octanol-Air	<input checked="" type="checkbox"/>	Vapor Pressure
Henry's Law	<input checked="" type="checkbox"/>	LogKoa: Octanol-Air
Index of Refraction	<input checked="" type="checkbox"/>	Henry's Law
Molar Refractivity	<input checked="" type="checkbox"/>	Index of Refraction
pKa Acidic Apparent	<input checked="" type="checkbox"/>	Molar Refractivity
Molar Volume	<input checked="" type="checkbox"/>	pKa Acidic Apparent
Polarizability	<input checked="" type="checkbox"/>	Molar Volume
	<input checked="" type="checkbox"/>	Polarizability
		Download

Property	Median		Range		Unit
	Experimental	Predicted	Experimental	Predicted	
LogP: Octanol-Water	3.32	3.24	3.32	2.40 to 3.73	-
Water Solubility	5.26e-04	1.58e-03	5.26e-04	5.70e-04 to 3.68e-03	mol/L
Density	-	1.14	-	-	g/cm^3
Melting Point	156	144	153 to 158	132 to 157	°C
Boiling Point	200	349	200	334 to 364	°C
Surface Tension	-	46.0	-	-	dyn/cm
Vapor Pressure	-	2.52e-07	-	7.01e-08 to 5.34e-07	mmHg
LogKoa: Octanol-Air	-	8.38	-	-	-
Henry's Law	-	6.96e-07	-	-	atm-m3/mole
Index of Refraction	-	1.60	-	-	-
Molar Refractivity	-	68.2	-	-	cm^3
pKa Acidic Apparent	-	10.3 (1)	-	10.3	-
Molar Volume	-	200 (1)	-	200	cm^3
Polarizability	-	27.0 (1)	-	27.0	Å^3

Physical Properties: OPERA Models



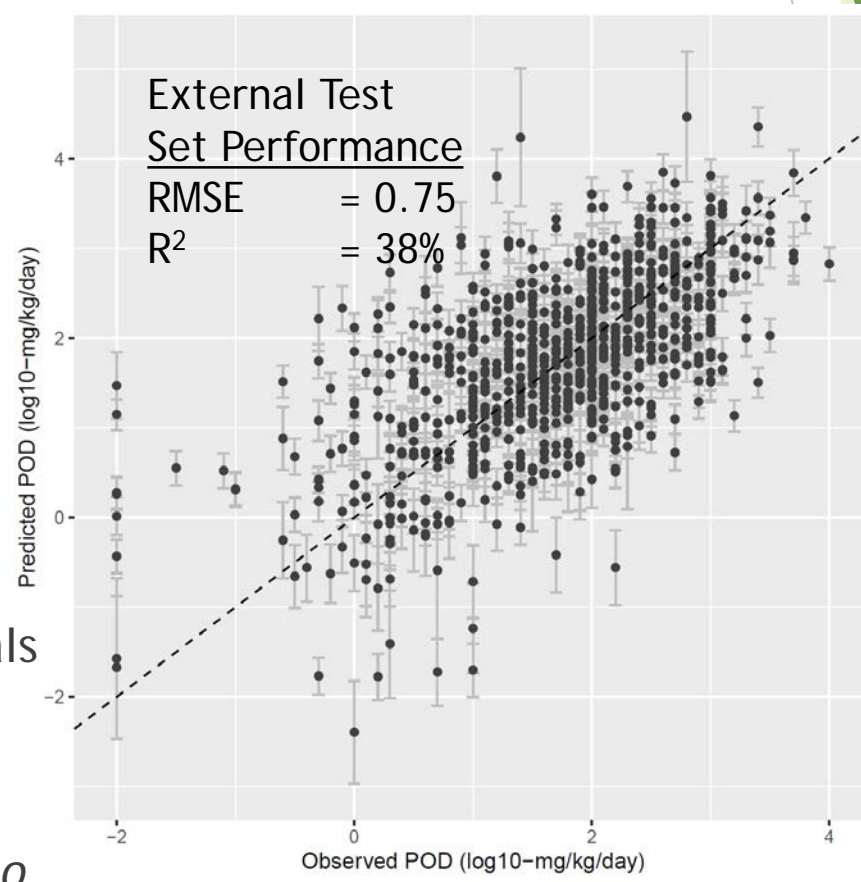
Model Performance
with full QMRF

Nearest Neighbors
from Training Set



Toxicity: Quantitative Predictions

- ▶ Systematic Point-of-Departure (POD)
- ▶ Input data:
 - ▶ In-vitro toxicity tests
 - ▶ Chemical properties
 - ▶ ToxCast bioactivity data
 - ▶ Toxicokinetic parameters
- ▶ Random Forest Regression Model
 - ▶ Training data: 3524 studies on 961 chemicals
 - ▶ 5 fold CV, 10x Bootstrapping
 - ▶ Predict a confidence interval for *lowest observed adverse effect level* (LOAEL) or *no observed adverse effect level* (NOAEL)





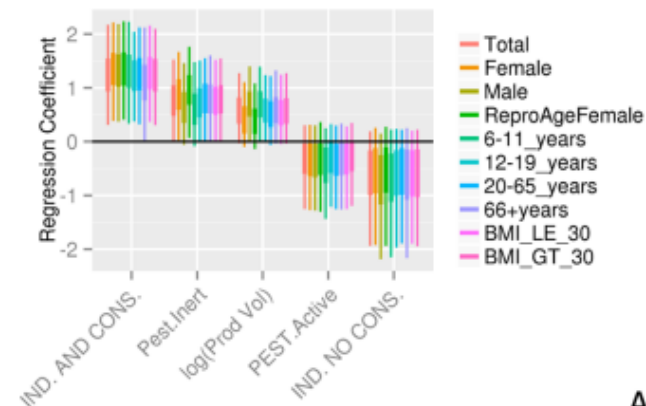
Exposure

Use Categories

- ▶ Existing use data
 - ▶ Regulatory classes
 - ▶ Product ingredient database
- ▶ Regression models to predict use if unknown
 - ▶ Structural and physical chemistry data

Exposure Predictions

- ▶ Wambaugh et al, 2014 - High throughput exposure model
- ▶ Linear regression based on physical properties, use data



Literature



Google Scholar

PubMed Abstract ...

PubChem Articles

PubChem Patents

PPRTV

IRIS

Select Term:

Dust and Exposure

Retrieve Articles

0 Articles

Edit the Query Before Retrieving Articles

("309-00-2" OR "Aldrin" OR "Aldrin") AND Dust AND Environmental Exposure

Add additional query terms to filter abstracts:

water

soil

Search and Count

wa...	soil	Te...	Total	PMID	Pu...	Title
0	0	0	0	23990271	2013	Organochlorine pesticides in the dust fall around Lake Chaohu, the fifth largest lake in China.
1	0	0	1	9460180	1998	Serum levels of several organochlorine pesticides in farmers correspond with dietary exposure and loc...

Record: 1 of 2

Title: Serum levels of several organochlorine pesticides in farmers correspond with dietary exposure and local use history.

Abstract: In response to reported increased cancer risks among farmers, the Agricultural Health Study (AHS) was designed to examine health outcomes and environmental exposures among farm families in the United States. In the pilot phase of the AHS, food, beverage, air, dermal, dust, surface wipe, and biological specimens (blood and urine) were collected and analyzed for six farm families in two states (IA and NC). In addition, questionnaires were administered to examine previous pesticide use. This paper reports the organochlorine pesticide results of the serum and dietary analyses as well as questionnaire results from the pilot exposure study of farmers and their families. Note, no organochlorine pesticides were reported as currently being applied to the study farms. In all human serum samples examined, typical U.S. population levels were found for the majority of the pesticides. In addition, human serum levels of organochlorine pesticides showed no significant daily or seasonal variation. However, serum trans-nonachlor levels were found to be higher in people living on the two farms in North Carolina than in people living on the four farms in Iowa ($p < 0.05$). Further, unusually high dieldrin levels were found in serum samples from a farmer and spouse living on an Iowa farm, and these levels were significantly higher than those of people living on the other farms ($p < 0.05$). Dieldrin was persistent in the foods consumed on the same Iowa farm where family members showed elevated serum levels. In addition, dietary samples from the North Carolina farms exhibited high

- ▶ Access to Google Scholar, PubMed, PubChem articles and patents, and IRIS assessments
- ▶ Abstract sifter lets users quickly search literature for pre-defined terms or add additional queries
- ▶ Sort and identify most relevant articles



Batch Searching

- ▶ Previous examples focused on reviewing one chemical at a time
- ▶ Batch search allows retrieval of data and model results for multiple chemicals

Batch Search?

Please enter one identifier per line

Select Input Type(s)

☐ Chemical Name

☐ CAS-RN

☒ InChIKey

☐ DSSTox Substance ID

☐ Exact Molecular Formula ?

Enter Identifiers to Search

GRWFGVWFFZKLT-IUCAKERBSA-N
WMBWREPUVVBILR-WIYYLYMNSA-N
CQUAYTJDLQBXCC-NHYWBVRUSA-N
RLLPVAHGXCWKJ-HKUYNNGSSA-N
OFCQYQOZASISIU-OGFXRTJISA-M
GRWFGVWFFZKLT-RKDXNWHRSA-N
XMGQYMWWDQXJH-UHFFFAOYSA-N
NETOHYFTCONDT-UHFFFAOYSA-N
XSXWOBXNULJG-UHFFFAOYSA-N
JLEHSYHLHLPAL-UHFFFAOYSA-N


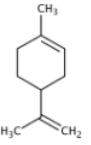
Display All Chemicals

Download Chemical Data



Batch Searching

- ▶ Previous examples focused on reviewing one chemical at a time
- ▶ Batch search allows retrieval of data and model results for multiple chemicals

Search Results								
Searched by List: Found 10 results.								
Download as: TSV Excel SDF								
ID ↑↓	Structure	Preferred Name ↑↓	CAS-RN ↑↓	QC Level ↑↓	CPCat...	Numb...	PubC...	Monoisotopi...
DTXSID20292 ToxCast™		(-)-alpha-Pinene	7785-26-4	Level 2: Exp...	1	42	61	136.125201
DTXSID20296 ToxCast™		Limonene	138-86-3	Level 2: Exp...	189	68	123	136.125201

Non-Targeted Analyses



- Supports high resolution mass spectrometry
- Mass and formula searching

Advanced Search?

Mass Search

Da \pm Da ppm

☒ Single component ☐ Ignore isotopes

Generate Molecular Formula(e)

Da \pm Da ppm

☒ Include halogens

Options ▾

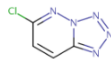
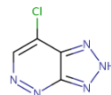
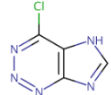
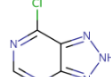
Molecular Formula Search

☒ Single component

Search Results

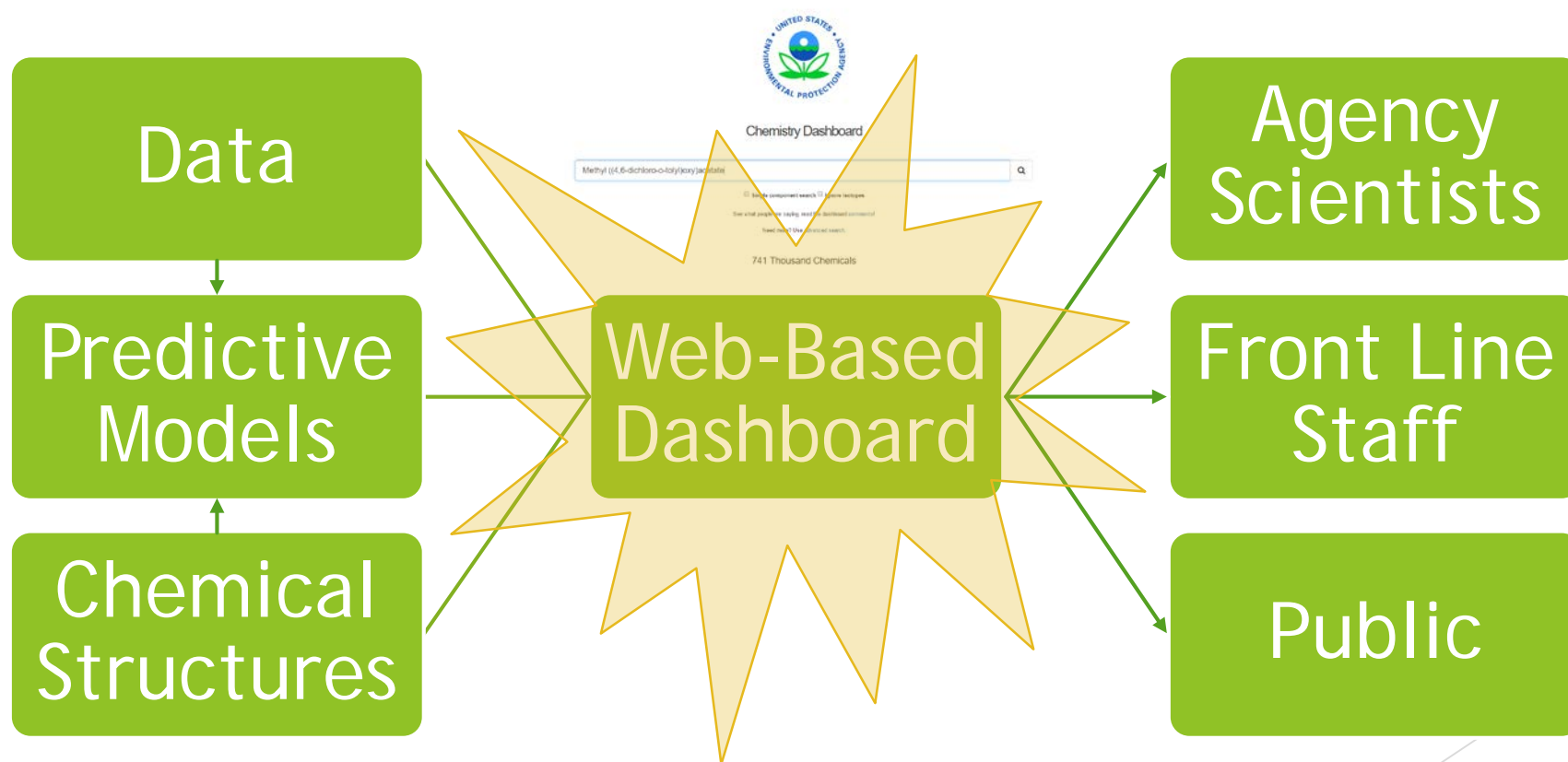
Download as: TSV Excel SDF

Searched by Mass and single component chemicals: Found 5 results for '155 ± 5 ppm'.

ID ↑↓	Structure	Preferred Name ↑↓	CAS-RN ↑↓	QC Level ↑↓	CPCat Count	Number of...	PubChem ...	Monoisotopic Mass ↑↓	Mass Differ...
DTXSID00307001		6-Chlorotetrazolo[1,5-b]pyridazine	21413-15-0	Level 5: Programm...	0	3	47	154.999873	-0.0001
DTXSID60393086		7-chloro-2H-triazolo[4,5-c]pyridazine	874-07-7	Level 5: Programm...	0	2	8	154.999873	-0.0001
DTXSID90420612		1H-imidazo[4,5-d]-1,2,3-triazine, 4...	52773-49-6	Level 5: Programm...	0	1	17	154.999873	-0.0001
DTXSID10651769		7-Chloro-2H-[1,2,3]triazolo[4,5-d]p...	23002-52-0	Level 5: Programm...	0	1	32	154.999873	-0.0001

McEachran et al, 2017: "Identifying known unknowns using the US EPA's CompTox Chemistry Dashboard"

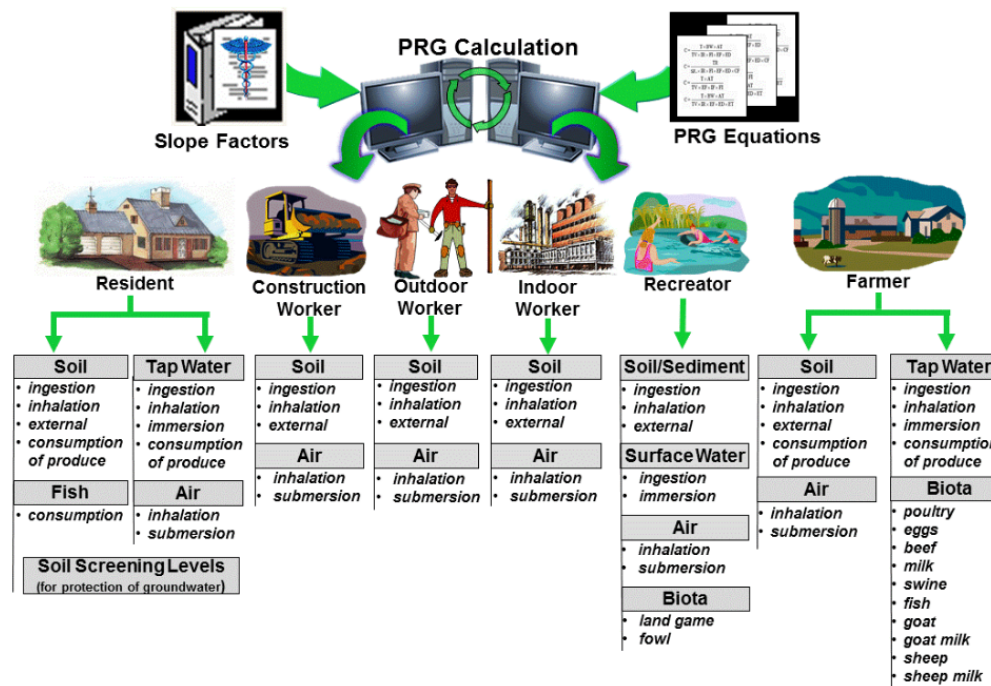
Dashboard



Putting it all together...

► Screening level calculations:

- Superfund specific policy
- Toxicity used to calculate “reference doses” (RfDs)
- RfDs are weighted with typical exposure assumptions
- May be used to screen sites, assess risk to human health





Next Steps

- ▶ Public version of the dashboard: <https://comptox.epa.gov/>
- ▶ Superfund specific customizations planned for internal beta testing, fall 2017
 - ▶ Cross validation with existing toxicity assessments (for models)
 - ▶ Understand how novel data sources can be used in the context of Superfund policy
- ▶ Future Work:
 - ▶ Completion and integration of predictive toxicity models
 - ▶ Enhanced visualization and interpretation of *in vitro* bioassay data
 - ▶ Workflow to calculate human health risks (following RAGS)
 - ▶ Structure, substructure, and similarity searching



Acknowledgements

- ▶ **EPA Office of Research and Development:** Antony Williams, Richard Judson, Imran Shah, Chris Grulke, Grace Patlewicz, Ann Richard, Andrew McEachran, Jon Sobus, Jason Lambert, Scott Wesselkamper, Nancy Baker, Jeff Edwards
- ▶ **EPA Office of Land and Emergency Management:** Stiven Foster, Kathleen Raffaele, Colette Hodes, Allaa Mageid, Rosalind Ramsey
- ▶ **EPA Regional Risk Assessors:** Wendy O'Brien, Kristen Keteles
- ▶ Questions?
 - ▶ Alicia Frame, OLEM/OSRTI - Frame.Alicia@epa.gov
 - ▶ Antony Williams, ORD/NCCT - Williams.Antony@epa.gov
 - ▶ Richard Judson, ORD/NCCT - Judson.Richard@epa.gov

Thank you!!