Development of a RapidTox Dashboard to Inform Risk Assessment

Jason C. Lambert, PhD, DABT
U.S. EPA, National Center for Computational Toxicology

Computational Toxicology Communities of Practice
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Outline of this presentation

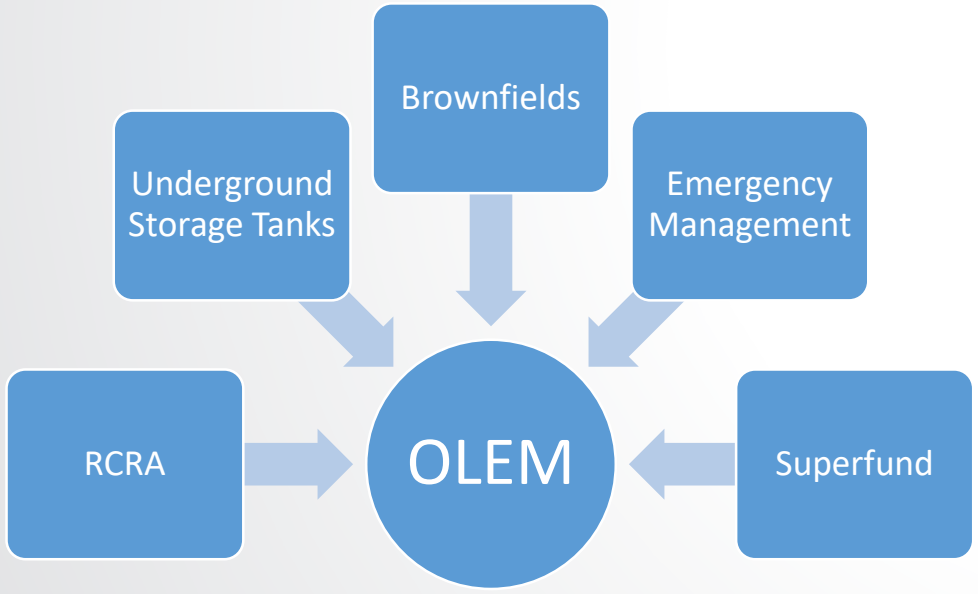
- Emergency Response and the U.S. EPA: brief overview
- Traditional Risk Assessment
  - Okay, Houston, we've had a problem here (Swigert, April 1970)
- CompTox Chemicals Dashboard
- RapidTox Prototype Workflow for Emergency Response

Background

- Decades of chemical production and use in product formulations
  - Pesticides, linear/(poly)cylic organics, complex materials (nano)
  - Consumer products, cosmetics, pharmaceuticals, textiles, etc. (e.g., CPSC, FDA)
- Occurrence in soil, water, air (rarely singular chemicals; mixtures)
- TSCA, FIFRA, CERCLA, SARA, RCRA
- Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA) and Superfund Amendments and Reauthorization Act (1986)
  - Superfund is an EPA program to clean up the most polluted sites in America
  - Sites are evaluated for risks to human health or the environment
  - Currently > 1300 NPL sites

Emergency Response and the U.S. EPA

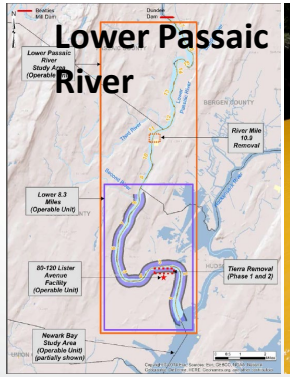
- Superfund is part of EPA's Office of Land and Emergency Management (OLEM) which responds to a wide variety of environmental risks



- **Emergency response:** Quick, reliable data to protect human health and the environment
- **Superfund Cleanups:** Robust toxicity data that can hold up in court
- **RCRA:** High quality hazard and physical properties data sufficient for regulations
- **All programs**:
  - UVCBs
  - Mixtures
  - Exposure
  - Fate and Transport, PhysChem

Emergency Response and the U.S. EPA

- 1000's of emergencies annually
  - Oil spills; release of chemical, biological, radiological, or nuclear contamination into the environment
- Scale of emergencies is diverse from localized/limited releases up to large-scale/national events
- Information needs for a given emergency scenario depends on the scope of the problem and the threat(s) involved (e.g., imminent threat to human health; intermediate phase(s); longer-term clean-up)

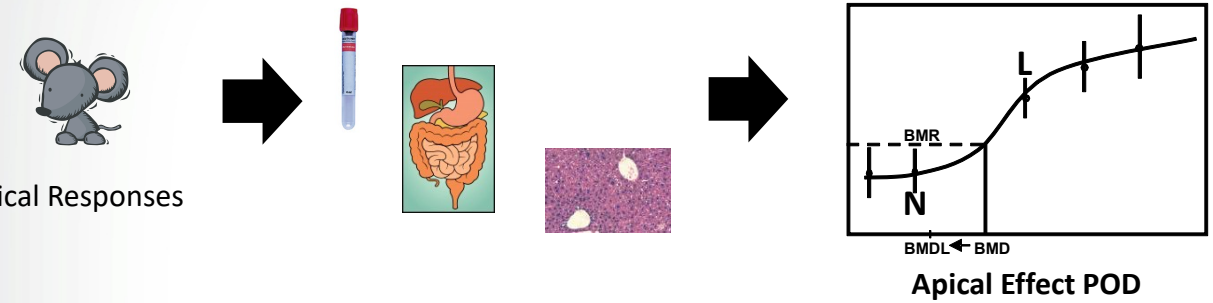




Emergency Response and the U.S. EPA

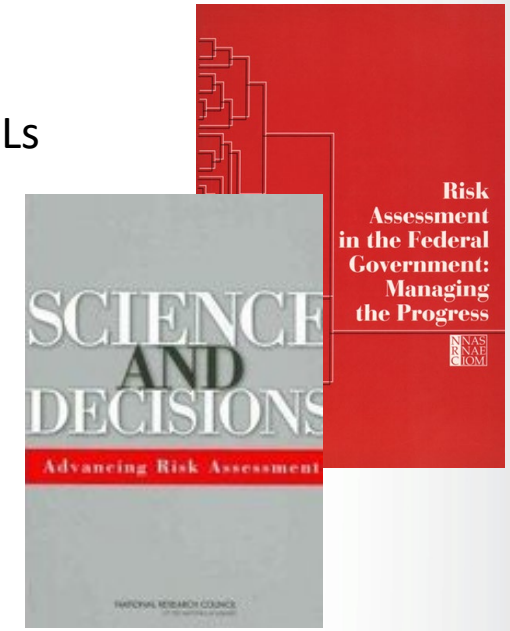
- Key reliance on existent health or toxicity values for exposure scenarios of concern (i.e., acute or short-term)
- Identification/use of values varies by response purview or condition (e.g., Regional Screening Level tables; AEGLs, CDC/NIOSH occupational values, NHSRC PALs, State-level values, etc.)
- No time to "come up" with health values for an emergency
  - Values available but for longer exposure duration(s)
  - No values at all; broad gradation of available toxicity data
- Option: wait for an assessment??? Can't wait—livelihood depends on rapid decisions
- Option: integrate existent information and new approach methodologies-based data to inform decision-making?
- What is the fit-for-purpose? Priority ranking, screening, and/or assessment

Traditional Risk Assessment Practice



Apical Effect POD

POD identification
-preferably BMDLs
-If BMD fails, NOAELs or LOAELs



- Non-cancer Reference Values (RfD, RfC) = POD/UF_C
- UF_C = composite uncertainty factor
  - UF_A = animal-to-human
  - UF_H = interindividual variability
  - UF_S = subchronic-to-chronic duration
  - UF_L = LOAEL-to-NOAEL
  - UF_D = database
- Cancer Values (OSF, IUR) = increased cancer risk from a lifetime oral or inhalation exposure to a chemical. Usually expressed in units of proportion (of a population) affected per mg/kg-day (oral) or $\mu g/m^3$ (inhalation)

Okay Houston, we've "got" a problem

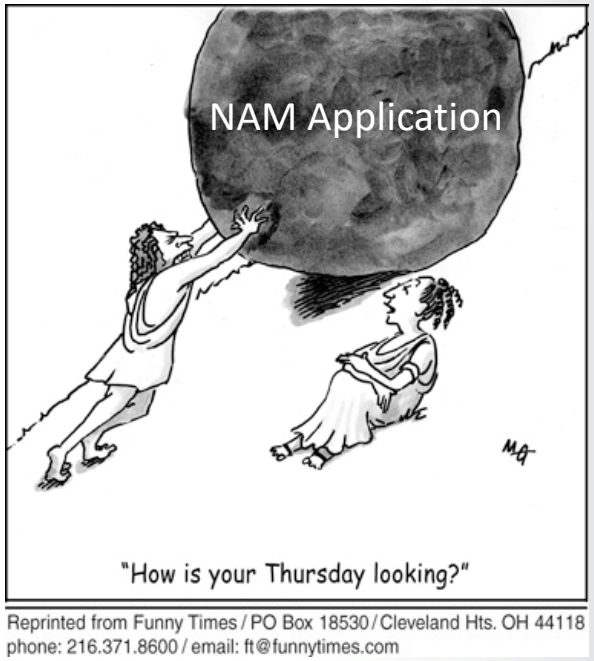
- Assessment timeline: Integrated Risk Information System (years), Provisional Peer-Reviewed Toxicity Values (months up to 2 years), ATSDR MRLs (years)
- Depending on who you talk to, there are anywhere from 20K to >80K chemicals currently in the environment/commerce
- Collectively, across our global community of toxicology and risk assessment practice, only a small fraction of those chemicals have been assessed for toxicity

*For problem formulations associated with protection of human health, in particular emergency response, higher throughput of qualitative and quantitative information for contaminants is paramount!

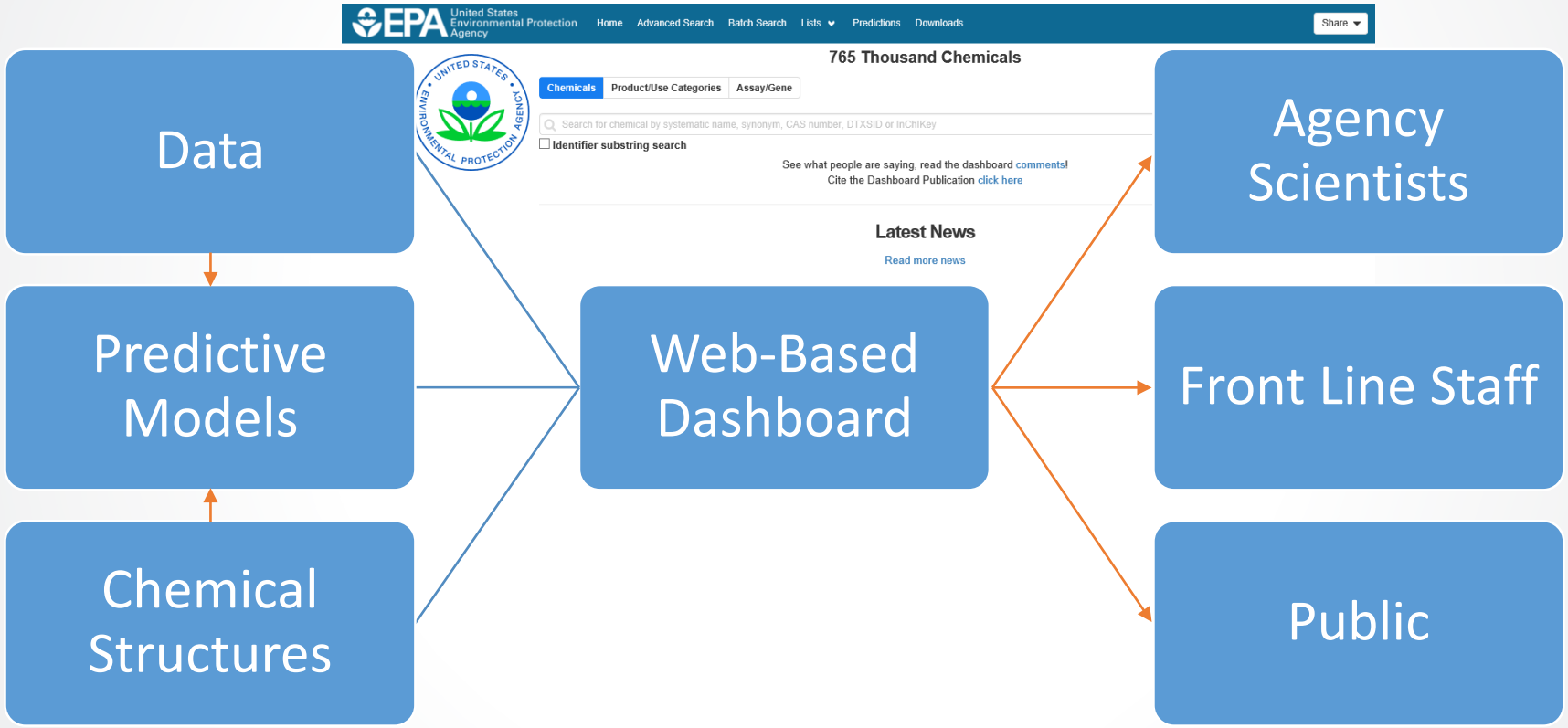
- Over the past decade, several reports, books, resource documents, etc. have been published regarding the use of New Approach Methods (NAM) across the human health risk assessment paradigm (i.e., shifting the paradigm)
- Numerous labs, centers, workgroups, and initiatives across federal, private, and academic institutions have been formed to advance NAM and Computational Toxicology platforms

NAM/CompTox Toolbox to Date

- **Data-mining**: comprehensive collection and collation of extant hazard and exposure data –(Martin et al. 2009. Environ Health Perspect 117: 392-399)
- **Chemoinformatics**: structure-activity/read-across; QSAR –(Wang et al. 2012. Regul Toxicol Pharmacol 63: 10-19; Helman et al. 2019. ALTEX Feb 4, epub ahead of print: https://www.altex.org/index.php/altex/article/view/1202)
- **High-Throughput (HT) Exposure modeling**: ExpoCast –(Egeghy et al. 2016. Environ Health Perspect. 124(6):697-702)
- **High-Throughput Toxicokinetics**: *in vitro-to-in vivo* (IVIVE) modeled dosimetry –(Wambaugh et al. 2015. Toxicol Sci 147: 55-67)
- **Bioactivity** (in vitro): cell-free and/or cell-based HT assay data –(Judson et al. 2011. Chem Res Toxicol 24: 451-462)
- **Adverse Outcome Pathway (AOP)**: expert-driven identification of signal transduction pathways along the exposure to outcome continuum. –(Edwards et al. 2015. J Pharmacol Exp Ther. epub ahead of print: http://jpet.aspetjournals.org/content/early/2015/11/04/jpet.115.228239.long)



EPA's CompTox Chemicals Dashboard



For more detailed info see: A.J. Williams et al. (2017). The CompTox Chemistry Dashboard: a community data resource for environmental chemistry. *J Cheminform* 9(1):61

CompTox Chemicals Dashboard Overview

Data Availability

- Chemical Properties
- Environmental Fate and Transport
- Hazard (*in vivo*, *in vitro*, *in silico*)
- ADME
- Exposure
- Bioactivity
- Similar Compounds
- Literature

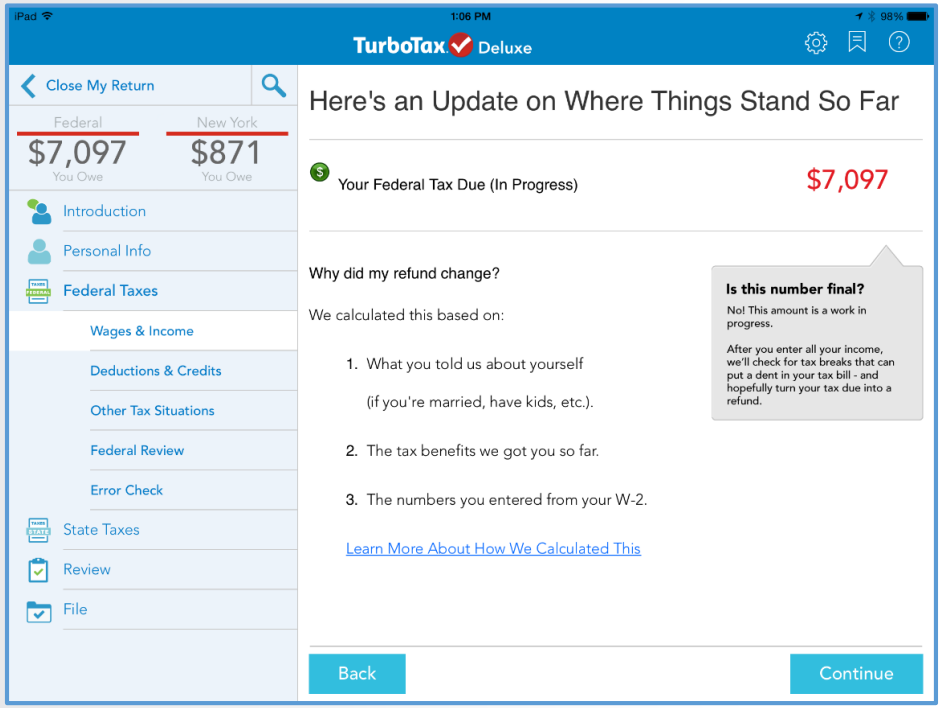
Data Interpretability/Application

- Key components:
  - Collects known health/tox/exposure values into one place
  - Readily surface hazard/D-R information (e.g., PODs)
  - Facilitates identification of analogue(s)
  - Can inform uncertainty(ies)
  - Fill information gaps
  - Linkable data streams

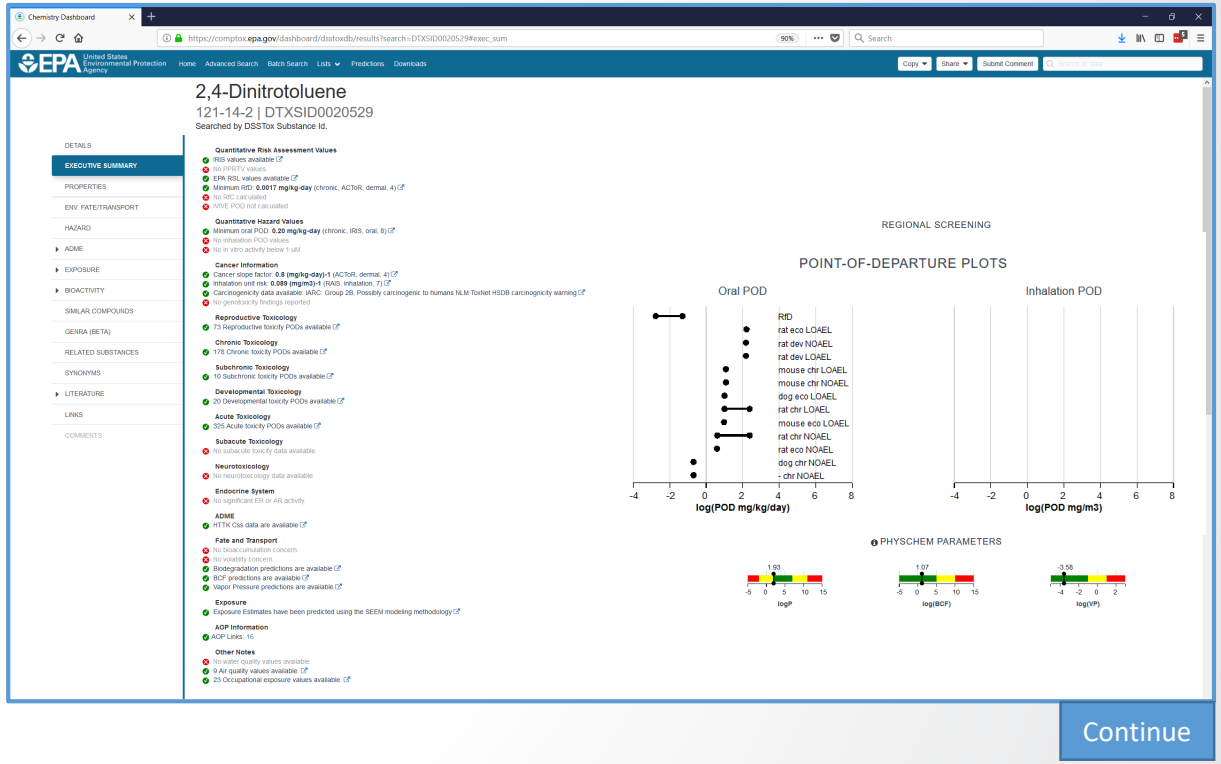
Current Public Dashboard: https://comptox.epa.gov/dashboard

What is RapidTox? An Analogy…

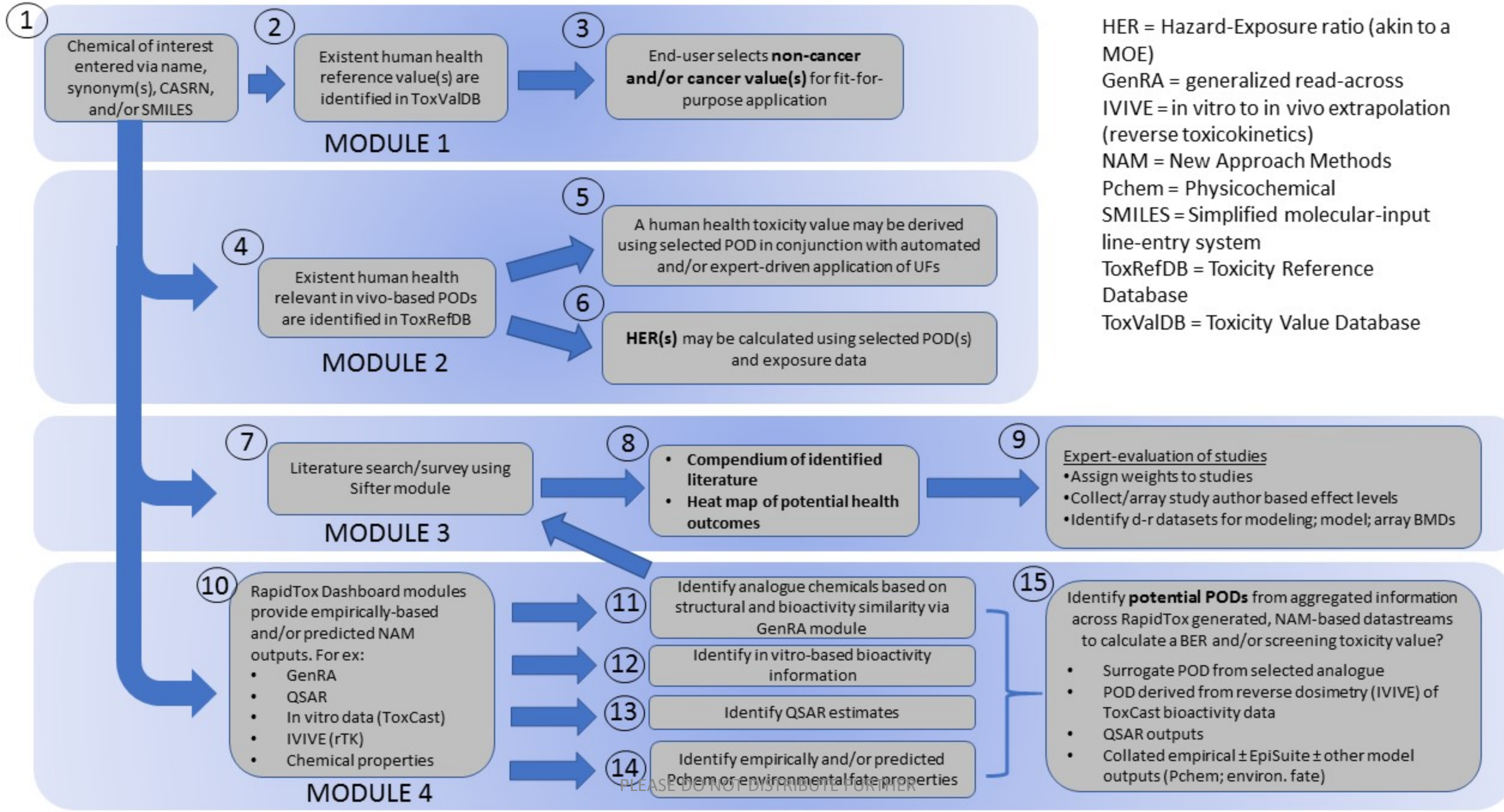
Workflow to Calculate Your Taxes



Workflows to Integrate Data for Regulatory Decisions



- RapidTox is a suite of workflows that facilitate the application of data surfaced in the CompTox dashboard in diverse assessment decision context



HER = Hazard-Exposure ratio (akin to a MOE)
GenRA = generalized read-across
IVIVE = in vitro to in vivo extrapolation (reverse toxicokinetics)
NAM = New Approach Methods
Pchem = Physicochemical
SMILES = Simplified molecular-input line-entry system
ToxRefDB = Toxicity Reference Database
ToxValDB = Toxicity Value Database

Hypothetical Emergency Response Scenario

- Multiple rail cars transporting semi-volatile organic materials involved in accident near major source waterway for local utility
- Seven compromised cars spill over 200,000 gallons of Hexadecanoic acid (CASRN 57-10-3), also known as palmitic acid, down an embankment into the waterway
- No RSL values; no IRIS, PPRTV, CalEPA, ATSDR or other known human health assessment/toxicity value
- Municipal and State governments issue call for support in dealing with the emergency; water utility intake shut down; information on hexadecanoic acid needed within 12 hrs

EPA United States Environmental Protection Agency

Home | Advanced Search | Batch Search | Lists | Predictions | Downloads

Chemistry Dashboard

Single Chemical Workflows

Emergency Response

Site-Specific Screening and Prioritization

Human Health Assessment

Multi-Chemical Workflows

Data Gathering

Prioritization

"click"

Discover.
About/Disclaimer
Accessibility
Privacy

Connect.
ACToR
DSSTox
Downloads

Ask.
Contact
Help

Step One Step Two Step Three Step Four Step Five Step Six
Step One: Select Input

Chemicals | Product/Use Categories | Assay/Gene

Hexadecanoic acid

Hexadecanoic acid
DTXSID20...

click

HEXADECANOIC ACID DER (FR. LAVANDULA) A
DTXSID50321651

HEXADECANOIC ACID NONYL ESTER
DTXSID30437345

Hexadecanoic acid--1-aminopropan-2-ol (1/1)
DTXSID30981959

Hexadecanoic acid--1,1'-azanediyldi(propan-2-ol) (1/1)
DTXSID401004744

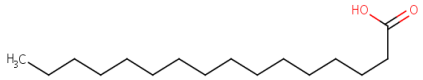
Hexadecanoic acid--1,1',1"-nitrilotri(propan-2-ol) (1/1)
DTXSID101004745

Hexadecanoic acid--2-(diethylamino)ethan-1-ol (1/1)
DTXSID80918098

Hexadecanoic acid--2,4a,8,9b-tetramethyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole (1/1)
DTXSID10914821

762 Thousand Chemicals

Hexadecanoic acid
57-10-3 | DTXSID2021602
Searched by DSSTox Substance Id.



Step One | Confirm Outputs | Step Three | Step Four | Step Five | Step Six

Emergency Response: Pre-populated Outputs and Additional User-defined Options

Emergency Response-Phase 1 Outputs (Pre-selected)

- ✓ Acute or Short-term Human Health values
- click → ⊘ Acute or Short-term Ecotoxicology values
- ✓ Subchronic or Chronic Human Health values
- click → ⊘ Subchronic or Chronic Ecotoxicology values
- ✓ Existent Points-of-Departure (all species)
- ✓ Physicochemical Properties
- ✓ Fate and Transport

(e.g., PAL, EL, MEG, TLV) ← hover

click → RUN

Additional Options Available (Pre-selected)

- ⊘ Literature Survey Heat Map
- ⊘ ToxCast/ToxPi profile
- ⊘ GenRA predictions
- ⊘ QSAR predictions

ToxVal type	Value	Units	Exposure route	Duration Class	Species	Source
Air quality standard (background)	10	mg/m^3	Inhalation	Chronic	-	DE AGOF Dust
Air quality standard (normal)	650	mg/m^3	Inhalation	Chronic	-	DE AGOF Dust
Air quality standard (attention value)	1500	mg/m^3	Inhalation	Chronic	-	DE AGOF Dust
Air quality standard (background)	10	mg/m^3	Inhalation	Chronic	-	DE AGOF SVOCs
Air quality standard (normal)	650	mg/m^3	Inhalation	Chronic	-	DE AGOF SVOCs
Air quality standard (attention value)	1500	mg/m^3	Inhalation	Chronic	-	DE AGOF SVOCs

Pre-Report Review (Emergency Response)

- Acute or Short-term human health values (**6**)
- Subchronic or Chronic Human Health values (**7**)
- Existent Points-of-Departure (in vivo all species)
- Physicochemical Properties
- Fate and Transport

Data Acquisitio

Generate Repor

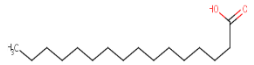
click

click

click

Acute or Short-term Human Health Values

Hexadecanoic acid
57-10-3 | DTXSID2021602
Searched by DSSTox
Substance Id.



Dossier: End-user session R8.11.20.18

Oral

Acute Oral Value(s):
Rat LD50 = 10,000 mg/kg

Inhalation

Acute Inhalation Value(s):
Protective Action Criteria-1 = 2 mg/m³
Protective Action Criteria-2 = 12 mg/m³

Existent Point-of-departure:

Fate and Transport:

Physicochemical Properties:

PLEASE DO NOT DISTRIBUTE FURTHER

Appendix A – Human Health Values

Oral-Acute/Short-term

ToxVal type	Value	Units	Exposure route	Duration Class	Species	Source
LD50	10000	mg/kg	Oral	Acute	Rat	Acute Tox

Oral-Subchronic

- There are no existent oral subchronic human health values for hexadecanoic acid (57-10-3)

Oral-Chronic

- There are no existent oral chronic human health values for hexadecanoic acid (57-10-3)

Inhalation-Acute/Short-term

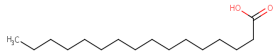
ToxVal type	Value	Units	Exposure route	Duration Class	Species	Source
PAC-1	2	mg/m³	Inhalation	Acute	-	DOE
PAC-2	12	mg/m³	Inhalation	Acute	-	DOE
PAC-3	12	mg/m³	Inhalation	Acute	-	DOE
Air quality standard	0.15	mg/m³	Inhalation	Acute (30 mins)	-	Canada Ontario JSL
Air quality standard	0.15	mg/m³	Inhalation	Acute (24 hrs)	-	Canada Ontario JSL

Inhalation-Subchronic

ToxVal type	Value	Units	Exposure route	Duration Class	Species	Source
MEG	50	mg/m³	Inhalation	Subchronic	-	DOD Air-MEGs Short-Term

Air quality	0.15	mg/m³	Inhalation	Acute (30	-	Canada

Hexadecanoic acid
57-10-3 |
DTXSID2021602
Searched by DSSTox Substance Id.



Step One — Step Two — Step Three — Step Four — Step Five — Step Six

Step Three: Data Availability Acquisition

Data Landscape for Output Generation-Emergency Response

Existent Toxicity Values

Information Availability | Evaluate Information

Points-of-Departure (in vivo)

Information Availability | Evaluate Information

Environmental Chemistry

● ○	PhysChem		
● ○	Fate and Transport	Review	Remove

Ecotoxicology Values

Information Availability		Evaluate Information	
○ ●	Acute/Short-term	Review	Select
○ ●	Subchronic/Chronic	Review	Select

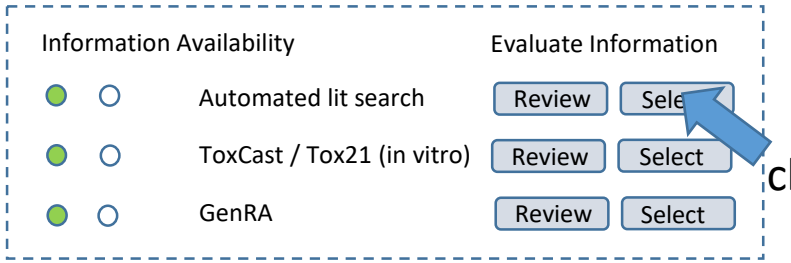
New Approach Methods

Information Availability		Evaluate Information	
● ○	Automated lit search	Review	Select
● ○	ToxCast / Tox21 (in vitro)	Review	Select
● ○	GenRA	Review	Select

Generate Pre-Report

Automated Literature search

New Approach Methods



- Pre-loaded boolean strings but can be customized

Abstract Sifter | Query PubMed | *Query run: hexadecanoic acid OR 57-10-3 AND toxicity*

v1.1 | Your sifter terms and frequency counts

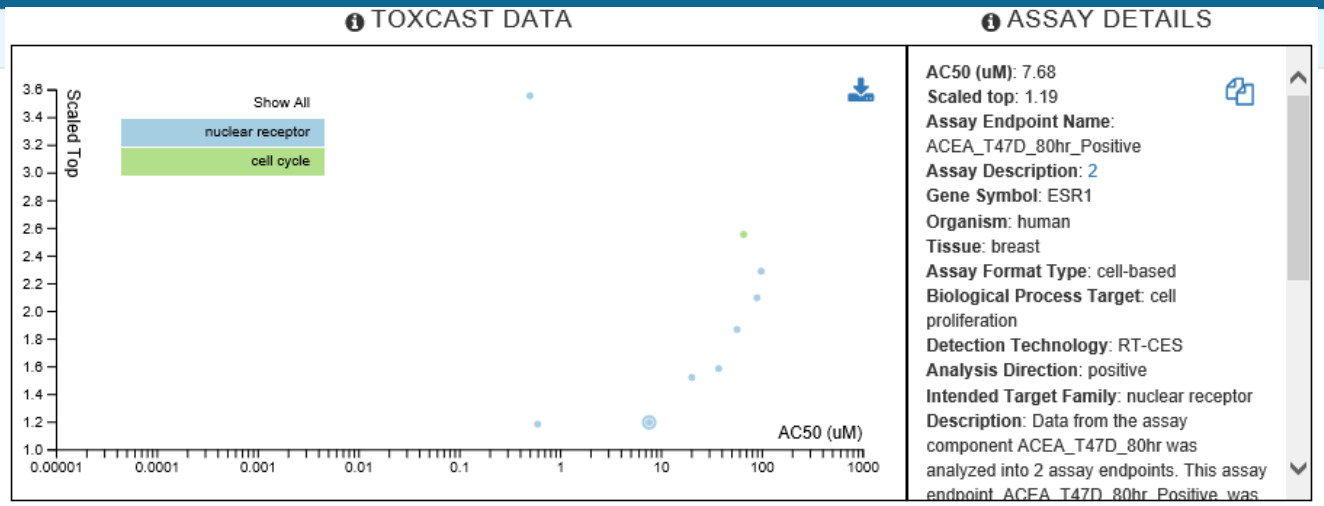
PMID	acute	toxicity	human	Total	Pub Yr	Title
30362416	0	1	0	1	2018	Lipids as activators of innate immunity in peptide vaccine delivery.
30333041	0	6	1	7	2018	Rosiglitazone ameliorates palmitic acid-induced cytotoxicity in TM4
30268793	1	1	3	5	2018	Toxicological evaluation of 2-dodecylcyclobutanone, a unique radio
30267964	0	0	0	0	2018	Differential surface contact killing of pristine and low EPS Pseudom
30255327	0	3	0	3	2018	GC-MS metabolomics reveals disturbed metabolic pathways in prim
30218681	0	5	1	6	2018	Graphene oxide nano-bio interaction induces inhibition of spermato
30208301	0	4	0	4	2018	Trigonelline prevents high cholesterol and high fat diet induced hep
30202233	1	2	0	3	2018	Anticandidal activity of the extract and compounds isolated from <i
30201523	0	3	0	3	2018	Development of an in vitro model to study hepatitis C virus effects
30194633	0	1	2	3	2018	Palmitic acid induces human osteoblast-like Saos-2 cell apoptosis v
30130541	0	1	0	1	2018	The traditional uses, phytochemistry, and pharmacology of Atractyl
30103897	0	5	3	8	2018	HAMSCs/HBMSCs coculture system ameliorates osteogenesis and
29940226	0	2	0	2	2018	Design and in vivo evaluation of entecavir-3-palmitate microcrystal
29925963	0	5	0	5	2018	Repellency, toxicity, and anti-oviposition of essential oil of Gardeni
29890411	0	2	1	3	2018	Analysis of proautophagic activities of Citrus flavonoids in liver cell
29853377	0	3	1	4	2018	Thermal degradation of agar: Mechanism and toxicity of products.
29730133	2	2	0	4	2018	Cytotoxic effect of Kalanchoe flammea and induction of intrinsic mi
29709653	0	3	1	4	2018	Oleic acid protects saturated fatty acid mediated lipotoxicity in hep
29705614	0	3	0	3	2018	Proteomic effects of repeated-dose oral exposure to 2-monochlorop
29704984	0	1	0	1	2018	Antibacterial activity of extracted bioactive molecules of Schinus te
29673862	0	1	0	1	2018	Chemical profiling of edible seaweed (Ochrophyta) extracts and as
29655752	1	4	1	6	2018	Systematic evaluation of phenolic compounds and protective capac
29606629	0	1	1	2	2018	Trans-Fats Inhibit Autophagy Induced by Saturated Fatty Acids.

Bioactivity

New Approach Methods

Information Availability			Evaluate Information	
●	○	Automated lit search	Review	Select
●	○	ToxCast / Tox21 (in vitro)	Review	Select
●	○	GenRA	Review	Select

click



	Modal	Description	SeqaPASS	Gene Name	AOP	Event	Hit Call	Top	Scaled Top	AC50	logAC50	Intended Target Family
_T47D_80hr_Negative		-	-	-	-	-	ACTIVE	54.9	2.55	66.5	1.82	cell cycle
_T47D_80hr_Positive		2	NP_000116.2	ESR1	200	1181	ACTIVE	29.1	1.19	7.68	0.885	nuclear receptor
ERE_CIS_up		75	NP_000116.2	ESR1	200	1181	ACTIVE	0.777	1.58	37.5	1.57	nuclear receptor
PPARa_TRANS_up		132	NP_005027.2	PPARA	58	468	ACTIVE	1.80	1.52	20.3	1.31	nuclear receptor
RORg_TRANS_up		-	NP_005051.2	RORC	-	-	ACTIVE	1.40	1.18	0.602	-0.220	nuclear receptor
XR_FXRSRC1_0480		753	NP_001193922.1	NR1H4	61	479	ACTIVE	52.1	2.09	90.2	1.96	nuclear receptor
XR_FXRSRC1_1440		754	NP_001193922.1	NR1H4	61	479	ACTIVE	93.4	2.29	99.2	2.00	nuclear receptor
ERa_LUC_BG1_Agonist		788	NP_000116.2	ESR1	200	1181	ACTIVE	90.2	3.55	0.505	-0.297	nuclear receptor
PXRE_CIS_dn		-	-	-	-	-	ACTIVE	1.25	1.86	57.2	1.76	nuclear receptor

Generalized read-across

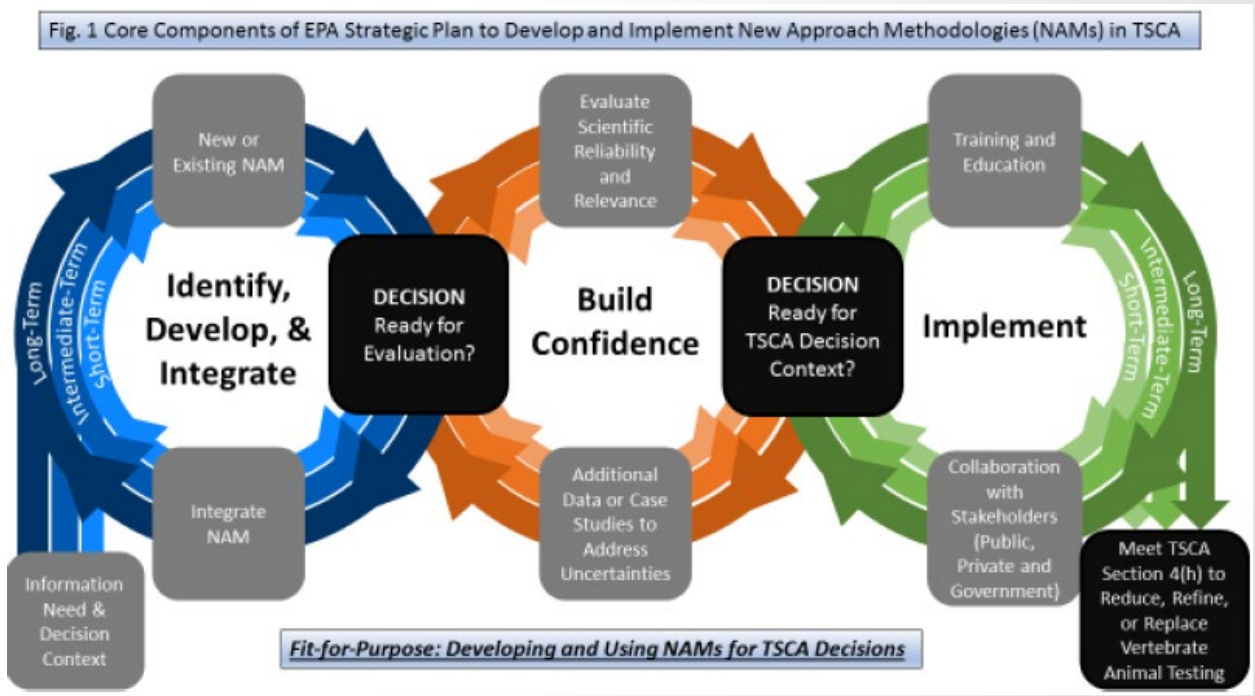
New Approach Methods

Information Availability			Evaluate Information	
●	○	Automated lit search	Review	Select
●	○	ToxCast / Tox21 (in vitro)	Review	Select
●	○	GenRA	Review	Sele

click

A Path Forward: Emergency Response and Beyond

- Early engagement with the end user community: define decision contexts from the beginning
- Iterative re-scoping of content and output structure based on end-user feedback
- Data producers, translators, and users work together
- Endgame: optimize workflow(s) and dashboard outputs



https://www.epa.gov/sites/production/files/2018-06/documents/epa_alt_strat_plan_6-20-18_clean_final.pdf

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- Questions?
  - Jason Lambert, ORD/NCCT – Lambert.Jason@epa.gov
  - Antony Williams, ORD/NCCT – Williams.Antony@epa.gov