

Safe and Sustainable Alternatives Program

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NTP Board of Scientific Counselors Meeting

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Safe and Sustainable Alternatives Program Team



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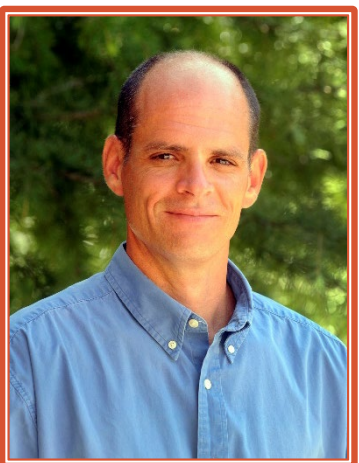
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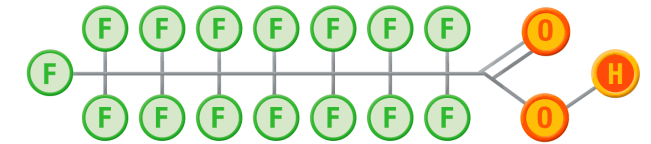
Regrettable substitutions & 'safer' alternatives, an ongoing problem

- Long history of replacing hazardous chemicals with other harmful chemicals

Original Chemical(s)	'Regrettable' Substitutions	
Lead arsenate	DDT	OP pesticides
BPA	Other bisphenols	?
PBB flame retardants	PBDE flame retardants	OP flame retardants
PFOS/PFOA	GenX	PFAS fluorotelomers

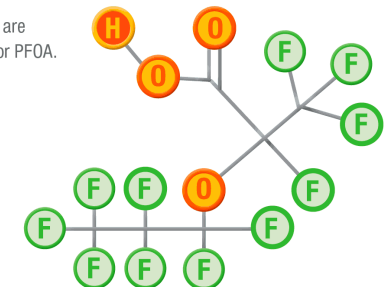
PFOA and PFOS chemicals

U.S. manufacturers voluntarily phased out PFOA and PFOS, two specific PFAS chemicals.



GenX chemicals

GenX chemicals are a replacement for PFOA.



- Marketed as 'safer' and 'better' despite limited information on the potential for toxicity or human health effects

<https://yourschwwater.com/pfas/>



Problem Formulation: Safer Alternatives



or



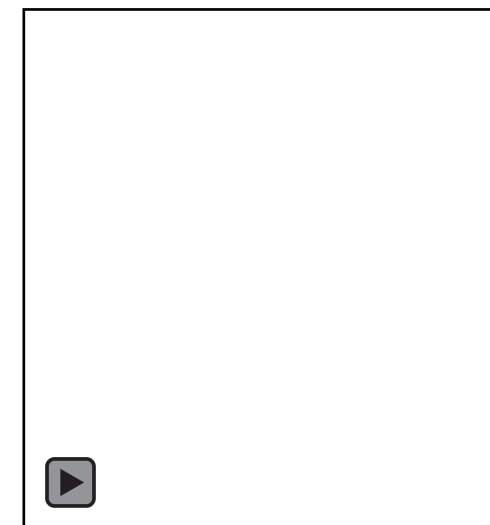
Unknown hazards



Hazard
identification



Chemical-by-chemical
approach



Metamorphosis of
Retrospective
Chemical-by-Chemical
Hazard Identification

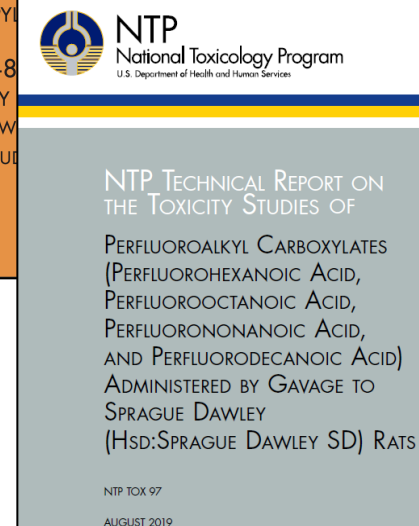
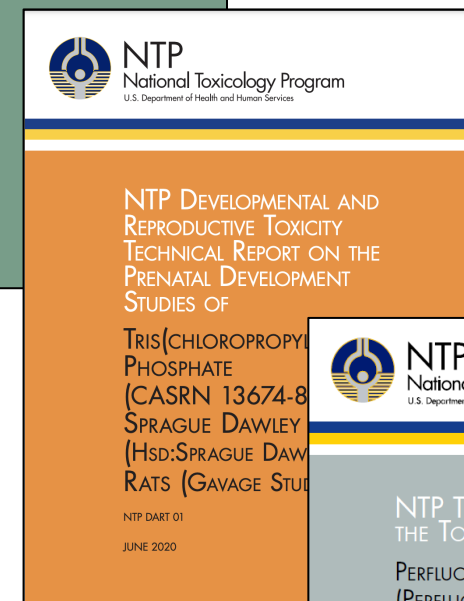
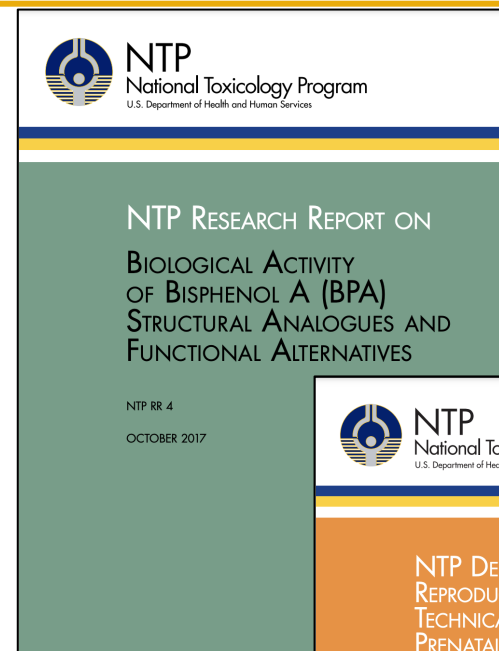


'Safer' chemical lists
Hazard contextualization
Exposure range scenarios





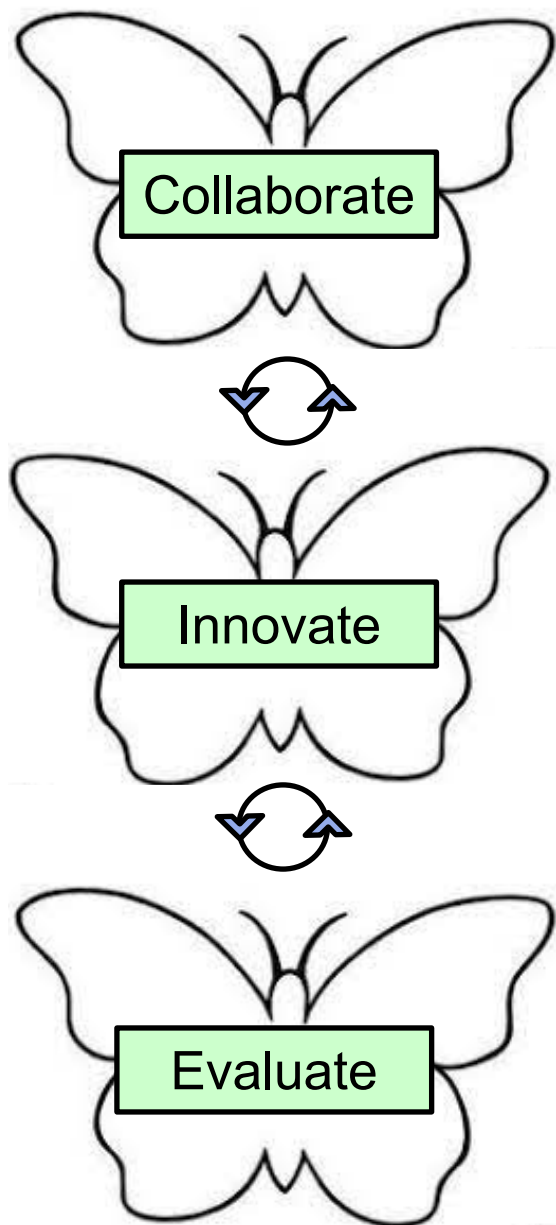
- DNTP's impactful history:
 - Chemical alternatives
 - Bisphenol analogues
 - Flame retardants
 - PFAS
 - Hazard identification, Absorption, distribution, metabolism & excretion (ADME), Tox21
 - Reactive vs. proactive: only after chemical is replaced
- Key question for SSA Program:
 - **How can DNTP help to end regrettable substitutions?**
 - Effectiveness (relevance, translation, context)
 - Efficiency (speed, coverage, automation)
 - Collaborate (tiered, fit-for-purpose communication)





Safe and Sustainable Alternatives Program





Objective 1

- Explore and establish stakeholder relationships and collaborations that identify critical gaps, opportunities, and strategies for proactive toxicological assessments of substances of public health concern.

Objective 2

- Identify and qualify effective tools and approaches through case studies that establish translational utility and refine proactive strategies for evaluation of alternative substances.

Objective 3

- Evaluate the relative potential for human health effects with exposures to select alternative substances.



Objective 1: Stakeholders and Partners

Explore and establish stakeholder relationships and collaborations that identify critical gaps, opportunities, and strategies for proactive toxicological assessments of substances of public health concern.

Regulatory Agencies



International Partners



Non-Governmental Organizations and Industry



CLEANGREDIENTS®





EPA Safer Choice: Safer Chemical Ingredients List

Safer Chemical Ingredients List

- The listed chemicals are safer alternatives, grouped by their [functional-use class](#).[†]
- Chemicals are marked as a  [green circle](#),  [green half-circle](#),  [yellow triangle](#), or  [grey square](#).[‡]
- This list includes many of the chemicals evaluated through the Safer Choice Program. It does not include confidential chemicals. There may be chemicals not included in this list that are also safer.
- Some of the listed chemicals may not be on the [TSCA inventory](#) and therefore may not be authorized/allowed for TSCA uses. Those considering TSCA uses for these chemicals should first determine whether such use is authorized. Chemicals not listed on the TSCA inventory are indicated as such in a pop-up box that appears upon clicking the hyperlinked CAS RN in the table below.

❖ Please Select: [All Functional Use Classes](#)

❖ or Select a Functional Use Class:

- [Antimicrobial Actives](#)
- [Chelating Agents](#)
- [Colorants](#)
- [Defoamers](#)
- [Emollients](#)
- [Enzymes and Enzyme Stabilizers](#)
- [Fragrances](#)
- [Oxidants and Oxidant Stabilizers](#)
- [Polymers](#)
- [Preservatives and Antioxidants](#)
- [Processing Aids and Additives](#)
- [Skin Conditioning Agents](#)
- [Solvents](#)



- Shift from “banned” lists only to identifying “safer” options
- **Most decisions on safety of chemicals are missing information on health effects**

-  **Green circle:** low hazard based on experimental or modeled data.
-  **Green half-circle:** expected to be of low hazard based on experimental or modeled data. Additional data would strengthen our confidence in the chemical's status.
-  **Yellow triangle:** met Safer Choice Criteria for its functional ingredient class, but has some hazard profile issues.
-  **Grey square:** not acceptable for use in products that are candidates for the Safer Choice label.

Adapted from EPA Safer Choice presentation (Davies et al.)



Groupings of GreenScreen® hazard endpoints



Human Health Group I	Human Health Group II	Human Health Group II*	Environmental Toxicity & Fate	Physical Hazards
Carcinogenicity (C)	Acute Mammalian Toxicity (AT)	Systemic Toxicity & Organ Effects – Repeated Exposure sub-endpoint (ST-repeated)	Acute Aquatic Toxicity (AA)	Reactivity (Rx)
Mutagenicity & Genotoxicity (M)	Systemic Toxicity & Organ Effects (ST-single)	Neurotoxicity – Repeated Exposure sub-endpoint (N-repeated)	Chronic Aquatic Toxicity (CA)	Flammability (F)
Reproductive Toxicity (R)	Neurotoxicity (N-single)	Skin Sensitization (SnS)	Other Ecotoxicity studies when available	Absorption Distribution Metabolism Excretion
		Respiratory Sensitization (SnR)		
Developmental Toxicity including Neurodevelopmental Toxicity (D)	Skin Irritation (IrS)		Persistence (P)	
	Eye Irritation (IrE)		Bioaccumulation (B)	
Endocrine Activity (E)				

Adapted from GreenScreen® v1.4 (Jan 2018)

- Key hazard considerations, prioritization schemes from stakeholders

- **How can we best generate information needed for decision-making?**

Objective 2

Identify and qualify effective tools and approaches through case studies that establish translational utility and refine proactive strategies for evaluation of alternative substances.



- ADME, human internal exposure, bioaccumulation
- In vitro and in silico screening to contextualize alternatives relative to established substances
- Innovative combinations of tools weaved into translational approach methods
- Case studies to qualify approaches, refine the context of application

Strengthening
Capabilities Programs



Collaborative Gap-filling

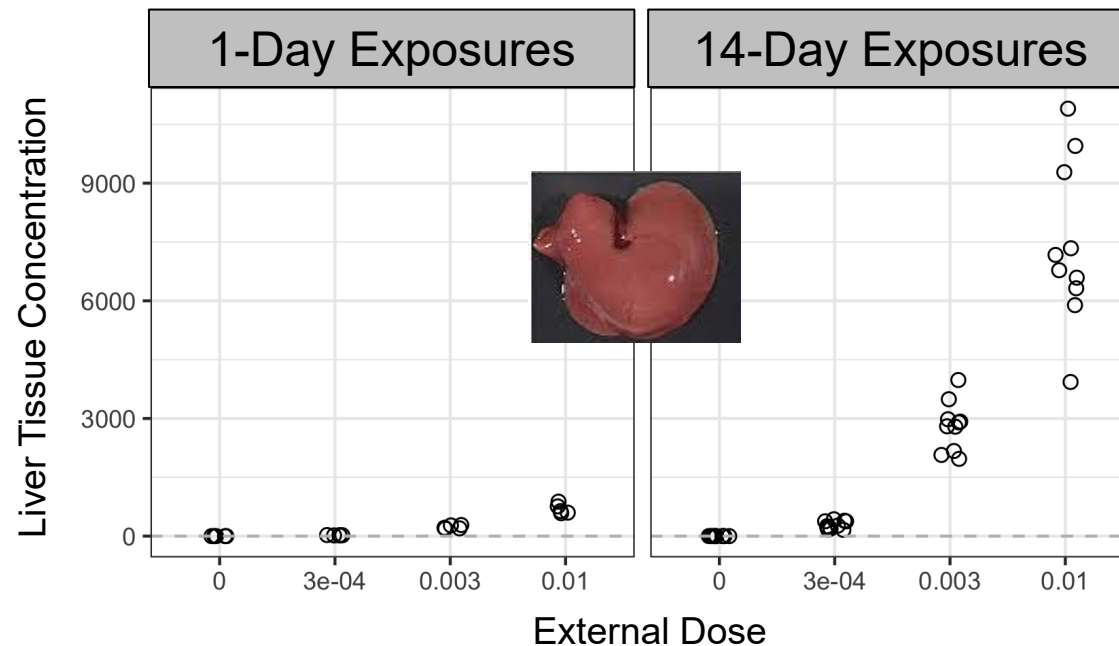


Objective 2: AFFFs and Bioaccumulation

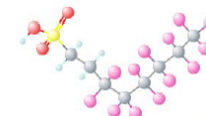


Key questions:

1. Do PFAS within presently-qualified AFFFs bioaccumulate in rat plasma or liver tissue?
2. What is the 'safer' ranking of AFFFs based on PFAS bioaccumulation?



6:2 Fluorotelomer Sulfonate (6:2 FTS)
TOXICOLOGY AT A GLANCE



6:2 FTS

- In 2012-2015, the U.S. metal plating industry transitioned from PFOS to short-chain fluorotelomers (e.g., 6:2) FTS in their chromium electroplating processes.
- The standard suite of tests conducted for regulatory approval of industry manufacture and use is available for 6:2 FTS.
- Based on currently available data, 6:2 FTS is less toxic and less persistent in the environment compared to PFOS and does not bioaccumulate.



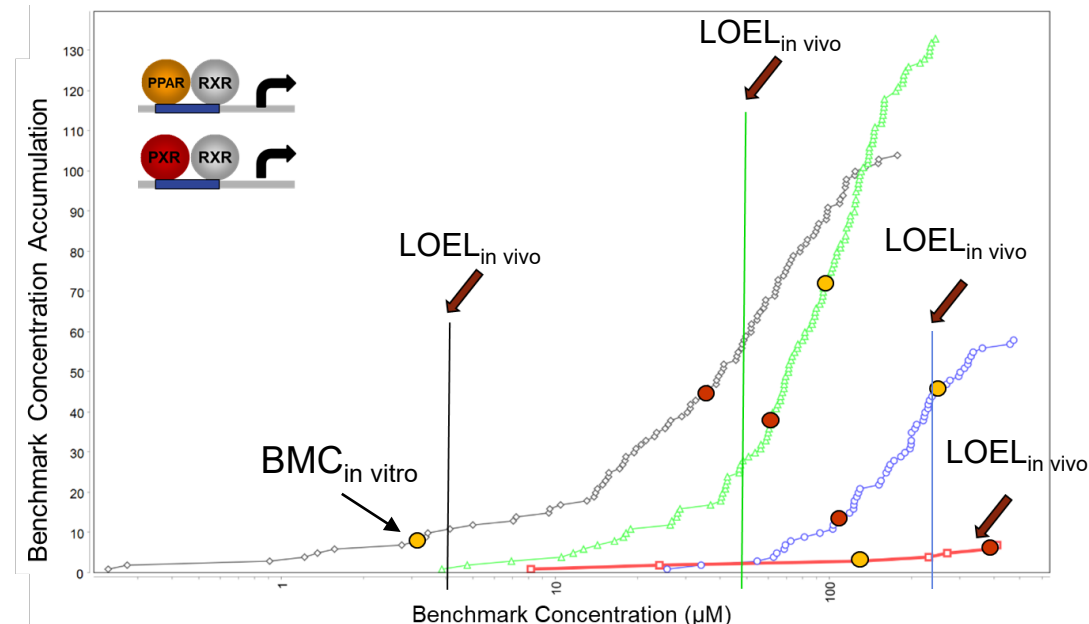
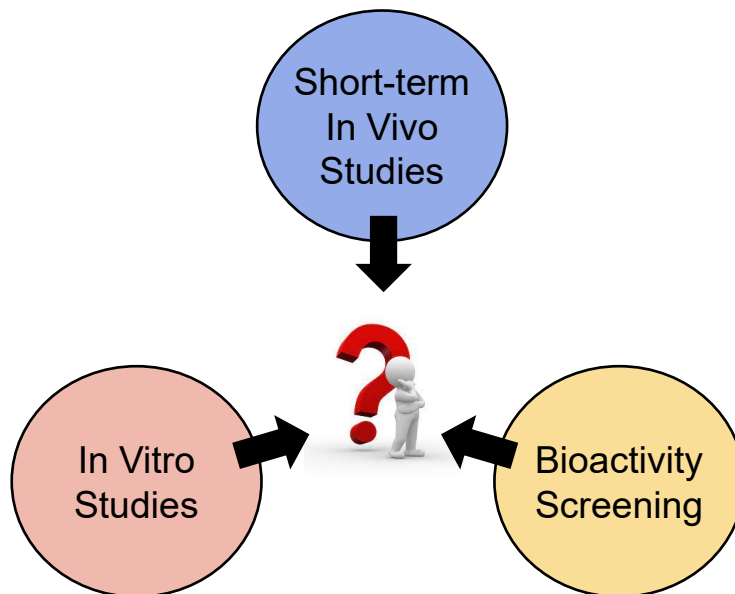


NTP
National Toxicology Program
U.S. Department of Health and Human Services

NTP TECHNICAL REPORT ON
THE TOXICITY STUDIES OF
PERFLUOROALKYL SULFONATES
(PERFLUOROBUTANE SULFONIC
ACID, PERFLUOROHXANE
SULFONATE POTASSIUM SALT, AND
PERFLUOROOCTANE SULFONIC ACID)
ADMINISTERED BY GAVAGE TO
SPRAGUE DAWLEY
(HSD:SPRAGUE DAWLEY SD) RATS

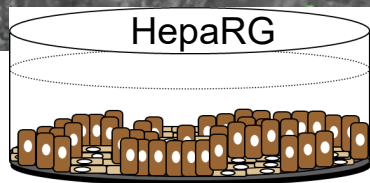
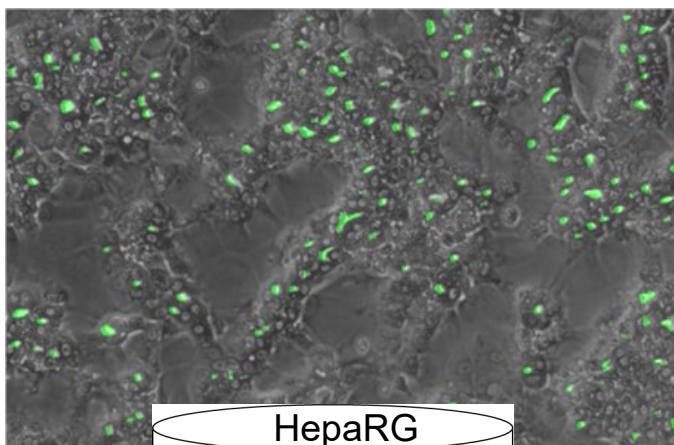
NTP TOX 96
AUGUST 2019

Objective 2: Data Integration for Human Translation



Key questions:

1. How can we enhance the human translation of DNTP investigations through data generation & integration?
 - $[\text{Chemical}]_{\text{blood}} \sim [\text{Chemical}]_{\text{culture media}}$
2. How effective are alternative toxicology methods to estimate the potencies toxicological response & make inferences to in vivo outcomes?
 - In vivo liver weight potencies (i.e., LOEL, lowest observable effect level) approximated by in vitro transcriptomic potency (i.e., $\text{BMC}_{\text{in vitro}}$, benchmark concentration)
 - Mechanisms in vivo $\sim$ in vitro biological response

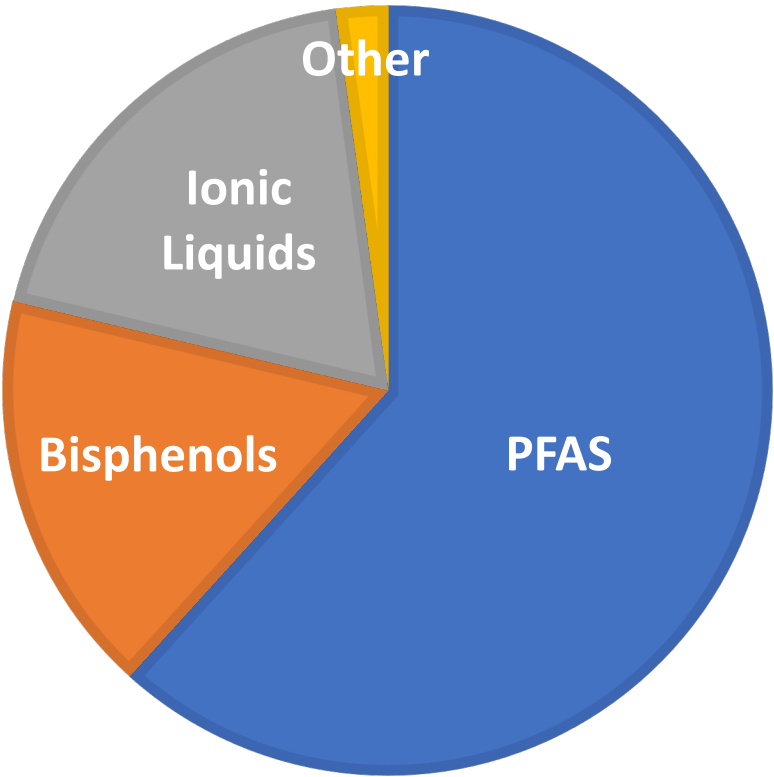




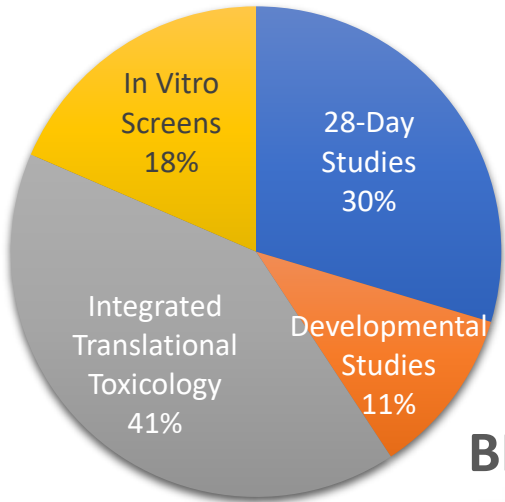
Evaluate the relative potential for human health effects with exposures to select alternative substances.

CURRENT PROJECT DISTRIBUTION

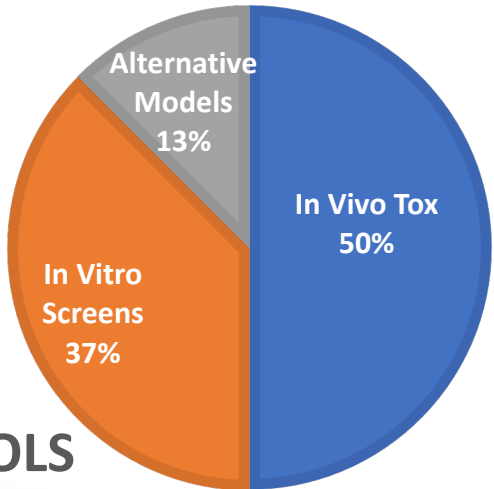
■ PFAS ■ Bisphenols ■ Ionic Liquids ■ Other



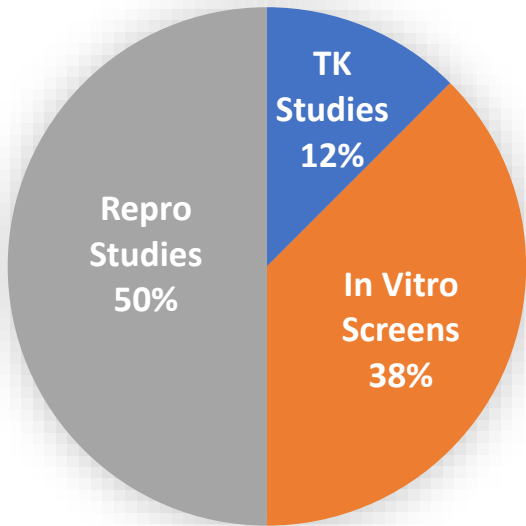
PFAS



IONIC LIQUIDS



BISPHENOLS

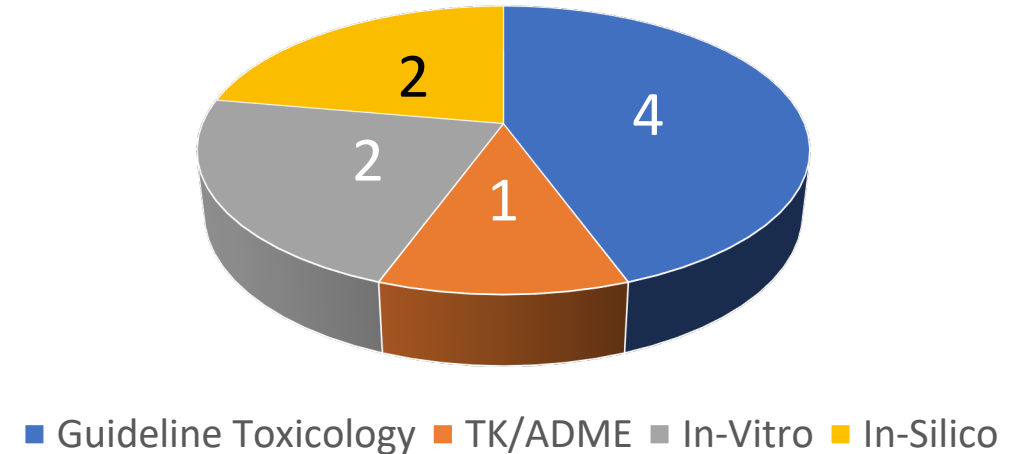




Objective 3: Bisphenols

- DNTP Activities
 - Literature review (24 analogues)
 - Analysis of Tox21/ToxCast bioactivity data
 - BPA analogues more similar to one another than estradiol
 - ADME-toxicokinetics: similar for BPS, BPAF, and BPA
 - BPS with moderately higher internal exposure
 - Maternal transfer demonstrated with BPAF
 - Modified One Generation Reproductive Toxicity with BPAF

Bisphenols Study Breakout

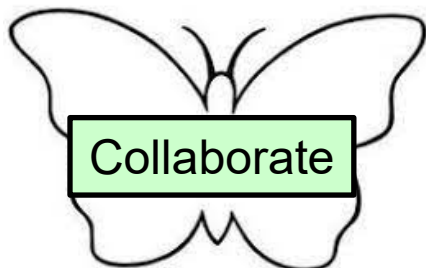


- What we've learned
 - Bisphenol analogues reveal similar concerns to BPA
 - Integrated assessments effective, enhanced opportunity for human translation

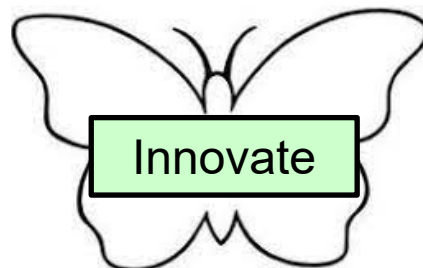


SSA PMT: Five-Year Strategy

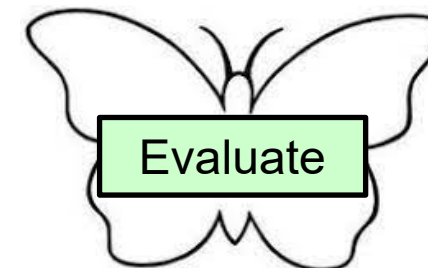
Objective 1



Objective 2



Objective 3



Short-term

- Dept. of Defense
- EPA Safer Choice
- EPA ORD CCED

- AFFF & PFAS
- Hepatic Bioaccumulation

- Reporting/closeout of legacy projects
- AFFF Manuscripts

Medium-term

- Review current strategies
- Identify Key Gaps

- PFAS-free AFFF Alternatives
- PFAS Bioaccumulation with MPS
- ID Innovations to Address Key Gaps

- 6,2-FTSA Dev Study
- Select PFAS Evaluations
- Identify critical data gaps

Long-term

- Establish Usable Frameworks & Action Trees
- SCRDA
- NDAA

- PFAS Mixtures Evaluations
 - renal/hepatic bioaccumulation
 - renal/hepatic toxicity
- Address Key Innovation gaps

- Complete 6,2-FTS Dev Study
- Project designs to address critical data gaps (PFAS)



What factors contributing to regrettable chemical substitutions represent promising scientific opportunities that the SSA research program can effectively address?



DNTP Project Leads and Staff

EPA's Safer Choice Program

EPA's Office of Research and Development

Clean Production Action

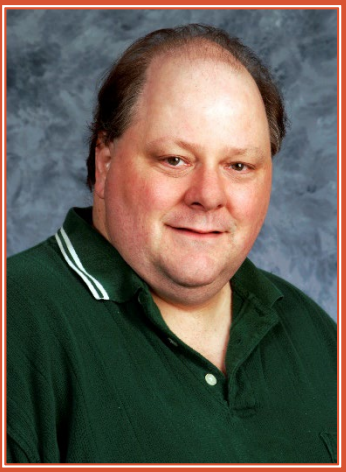
Department of Defense

Thank You!





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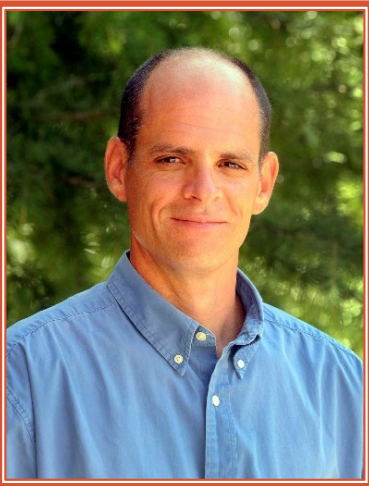
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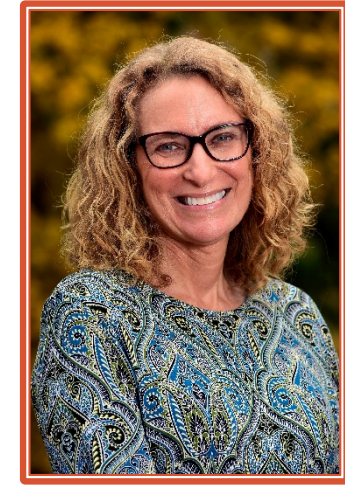
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Abbreviations and Acronyms

6,2-FTSA	6,2-fluorotelomer sulfonic acid
AFFFs	aqueous film forming foams
BPA	bisphenol A
BPAF	bisphenol AF
BPS	bisphenol S
DDT	dichlorodiphenyltrichloroethane
EPA ORD CCED	Environmental Protection Agency Office of Research and Development Chemical Characterization and Exposure Division
GenX	2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3- heptafluoropropoxy) propanoic acid
MPS	microphysiological systems
NDAA	National Defense Authorization Act
OP	organophosphate
PBB	polybrominated biphenyl
PBDE	polybrominated diphenyl ether
PFAS	per- and polyfluoroalkyl substances
PFOA	perfluorooctanoic acid
PFOS	perfluorooctanesulfonic acid
SCRDA	Sustainable Chemistry Research and Development Act
TK	toxicokinetic