NTP National Toxicology Program

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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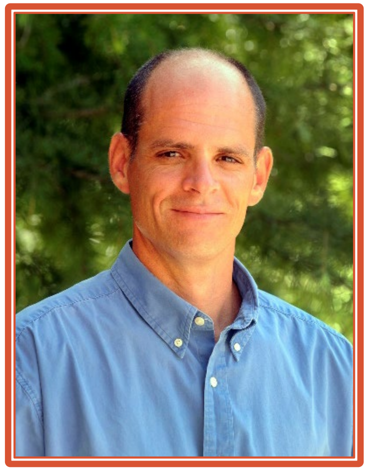

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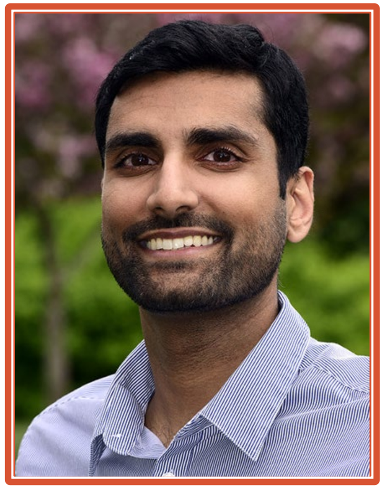

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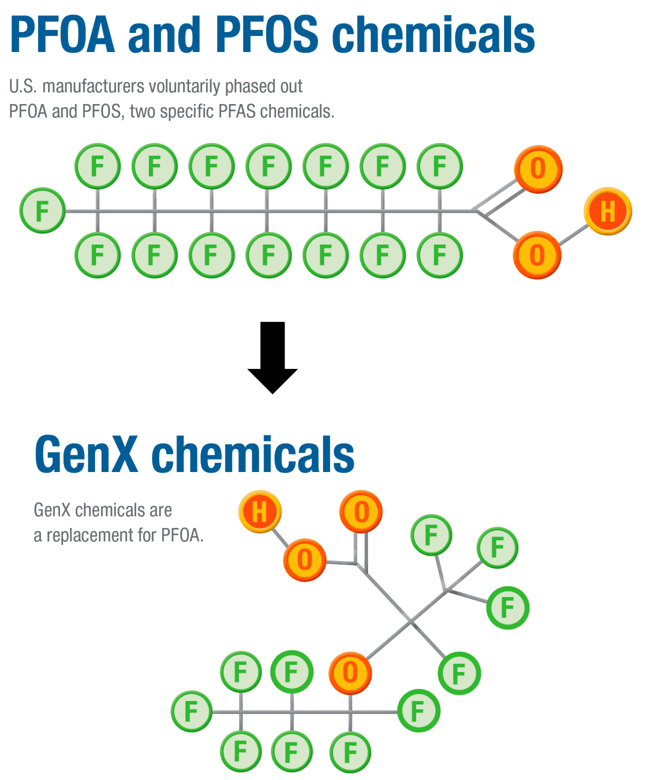
Regrettable substitutions & 'safer' alternatives, an ongoing problem

- 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



https://yourscvwater.com/pfas/

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

Problem Formulation: Safer Alternatives

or

Unknown hazards

Hazard identification

Chemical-by-chemical approach

Metamorphosis of Retrospective Chemical-by-Chemical Hazard Identification

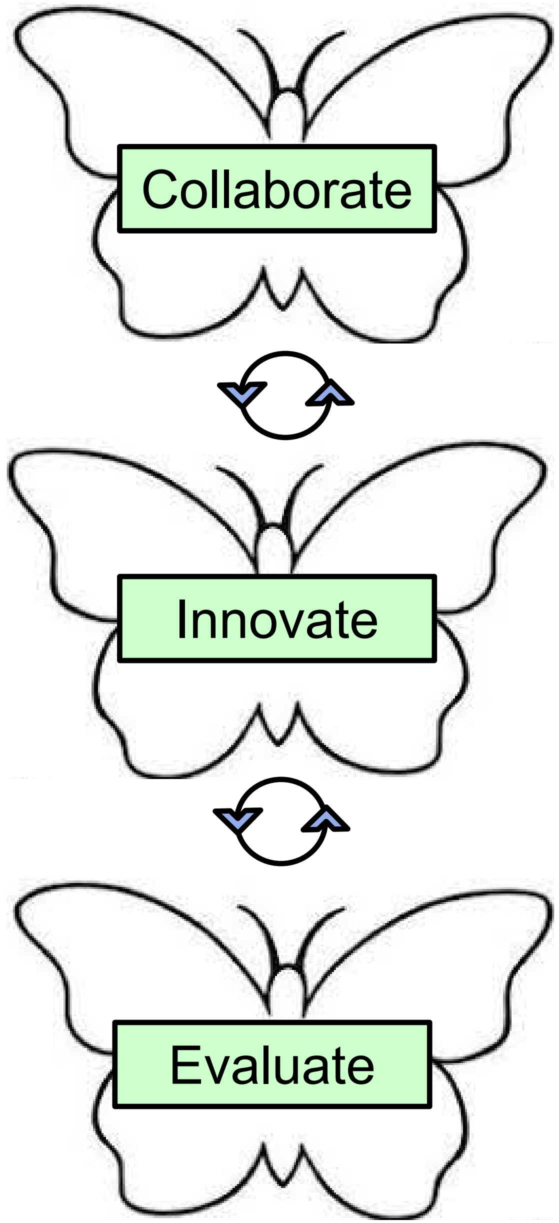
‘Safer’ chemical lists
Hazard contextualization
Exposure range scenarios

NTP and Alternatives

- DNTP’s impactful history:
  - Chemical alternatives
    - Bisphenol analogues
    - Flame retardants
    - PFAS
  - Hazard identification, Absorption, distribution, metabolism & excretion (ADME), Tox21
  - Reactive vs. proactive: only <u>after</u> 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

Program Objectives



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

OSHA®

OEHHA
California Office of Environmental Health Hazard Assessment

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Design for the Environment U.S. EPA

SAFER CHOICE
Meets U.S. EPA Safer Product Standards
epa.gov/dfesaferchoice

International Partners

ECHA
EUROPEAN CHEMICALS AGENCY

OECD

Non-Governmental Organizations and Industry

ASSOCIATION FOR THE ADVANCEMENT OF ALTERNATIVES ASSESSMENT

CLEANGREDIENTS®

GREENSCREEN® FOR SAFER CHEMICALS

BizNGO
FOR SAFER CHEMICALS & SUSTAINABLE MATERIALS

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

SAFER CHOICE
Meets U.S. EPA Safer Product Standards
epa.gov/dfesaferchoice

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

- 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.

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	
		Respiratory Sensitization (SnR)		
Developmental Toxicity including Neurodevelop-mental Toxicity (D)	Skin Irritation (IrS)		Persistence (P)	
	Eye Irritation (IrE)		Bioaccumulation (B)	
Endocrine Activity (E)				

Absorption
Distribution
Metabolism
Excretion

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 <u>internal</u> 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

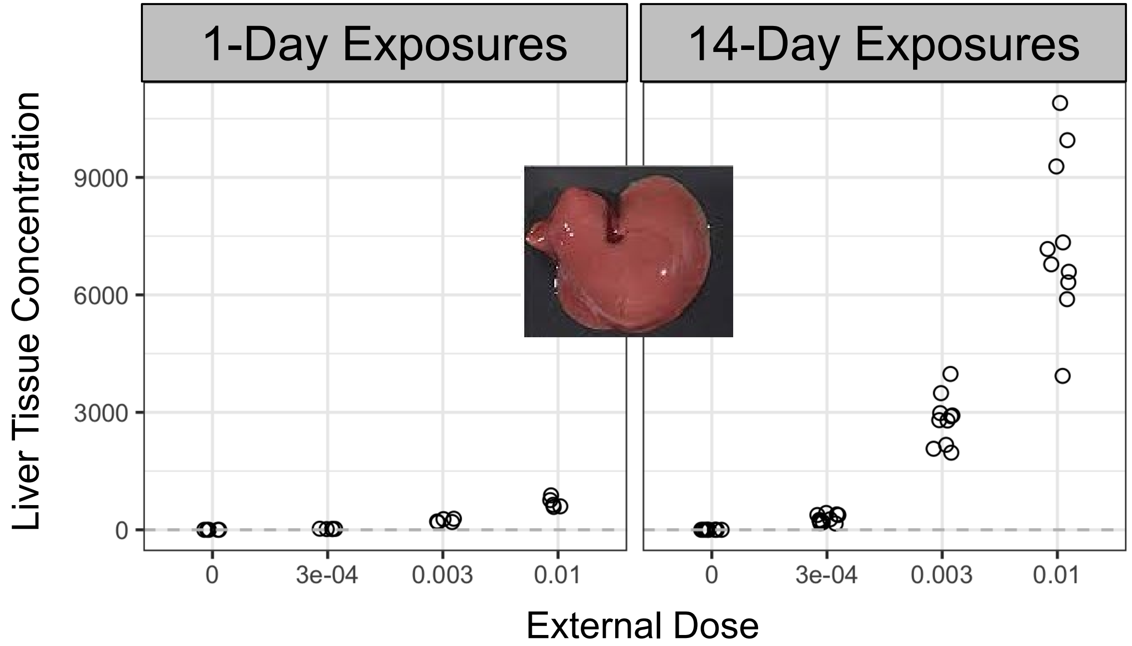
Collaborative Gap-filling

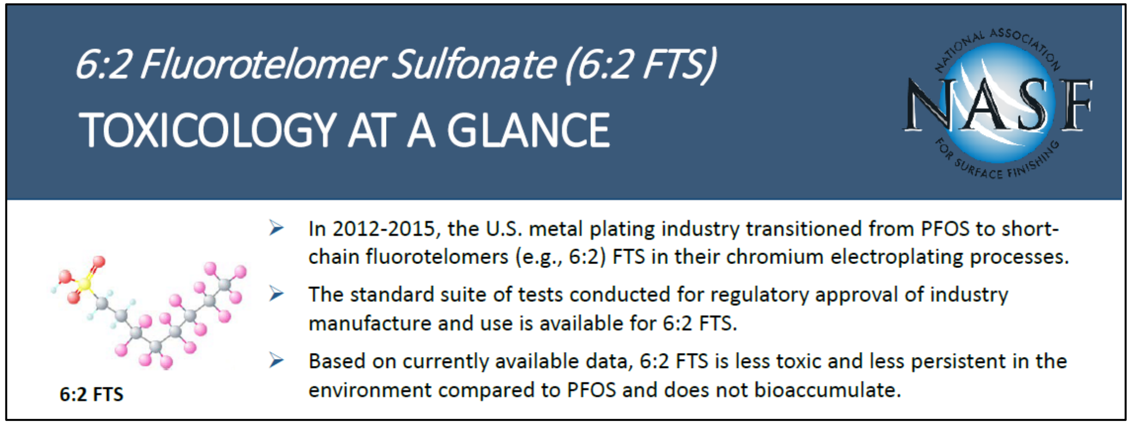
Objective 2: AFFFs and Bioaccumulation

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?





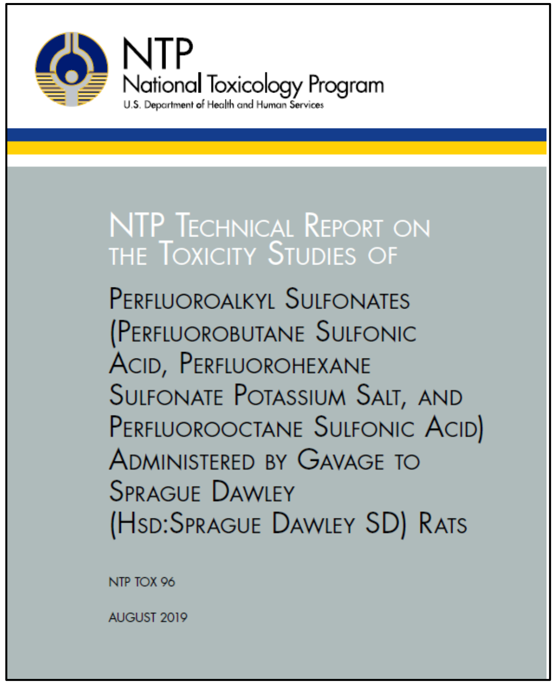
6:2 Fluorotelomer Sulfonate (6:2 FTS)

TOXICOLOGY AT A GLANCE

- 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.

6:2 FTS

Objective 2: Data Integration for Human Translation

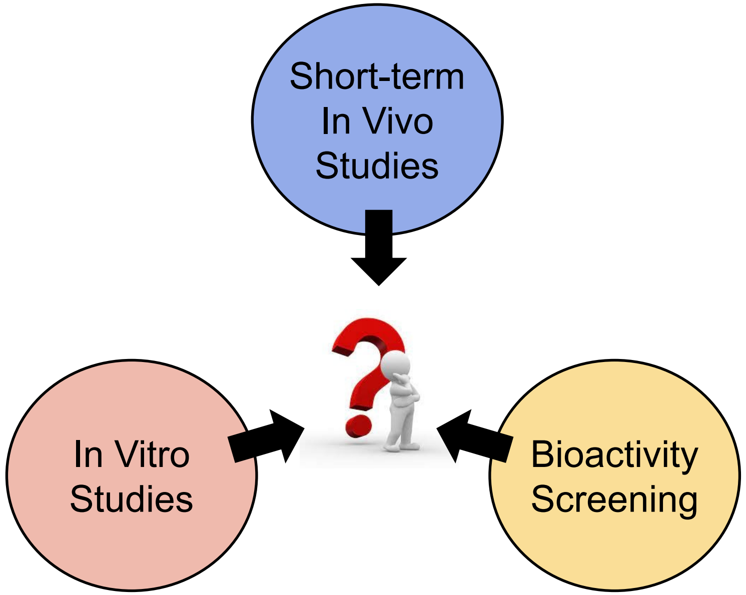

NTP
National Toxicology Program
U.S. Department of Health and Human Services

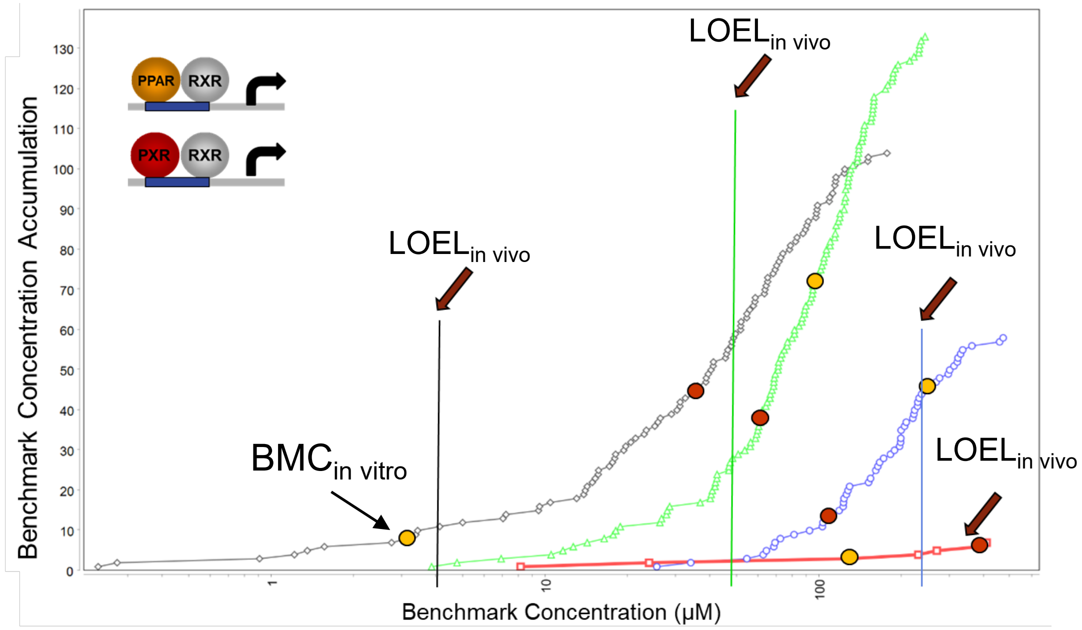
NTP Technical Report on the Toxicity Studies of

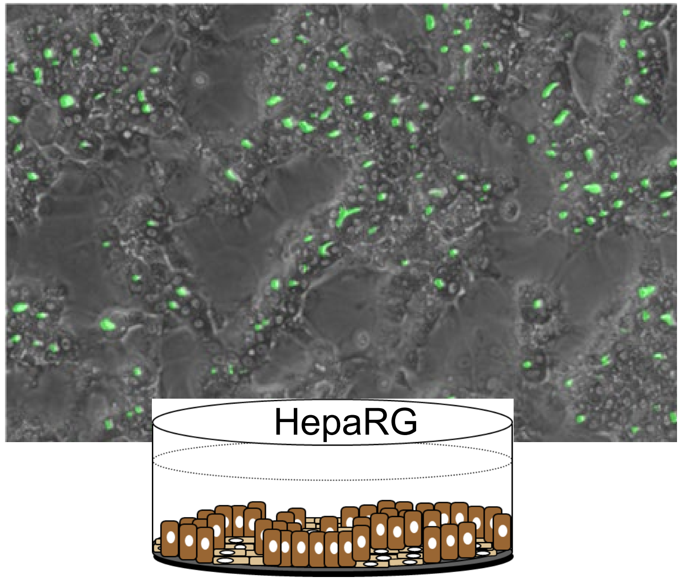
Perfluoroalkyl Sulfonates (Perfluorobutane Sulfonic Acid, Perfluorohexane Sulfonate Potassium Salt, and Perfluorooctane Sulfonic Acid) Administered by Gavage to Sprague Dawley (Hsd:Sprague Dawley SD) Rats

NTP TOX 96

August 2019







<u>Key questions:</u>

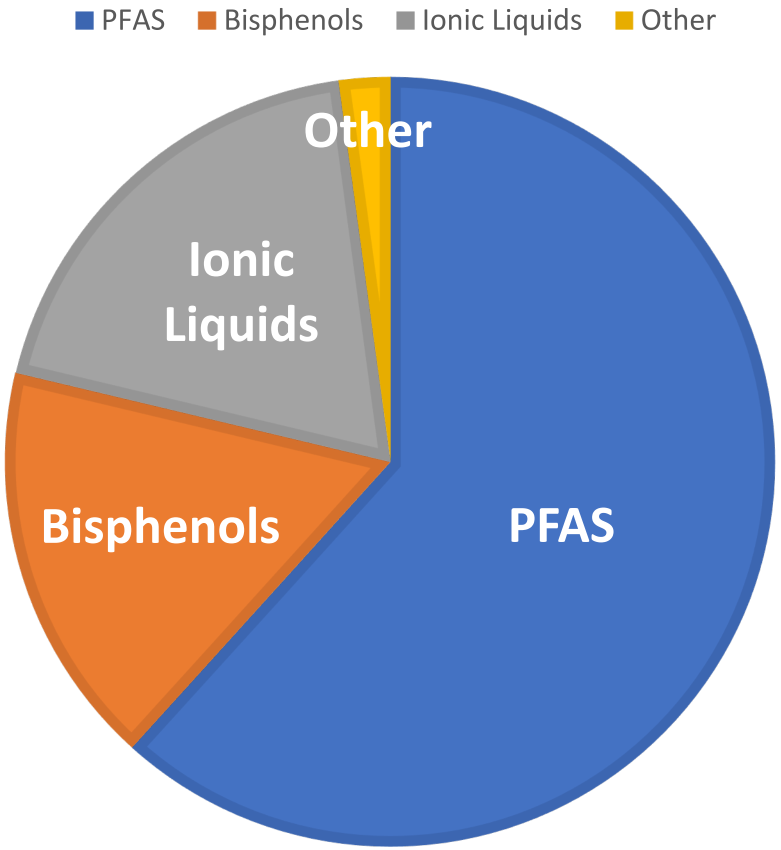
1. How can we enhance the human translation of DNTP investigations through data generation & integration?
   – $[\text{Chemical}]_{blood}$ ~ $[\text{Chemical}]_{culture\ media}$

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., BMC$_{in\ vitro}$, benchmark concentration)
   – Mechanisms in vivo ~ in vitro biological response

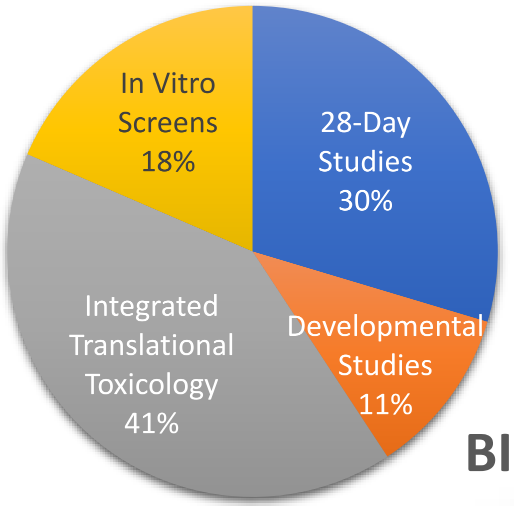
Objective 3

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

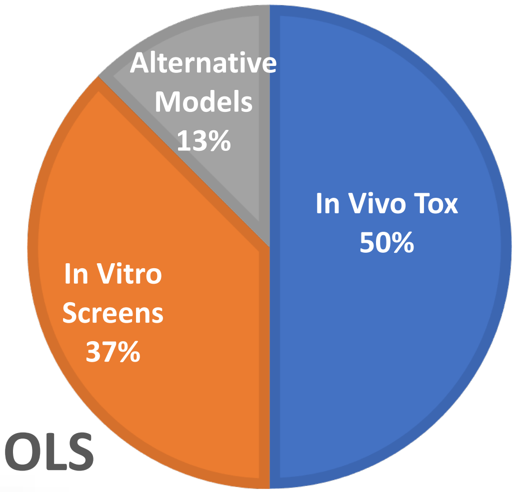
CURRENT PROJECT DISTRIBUTION



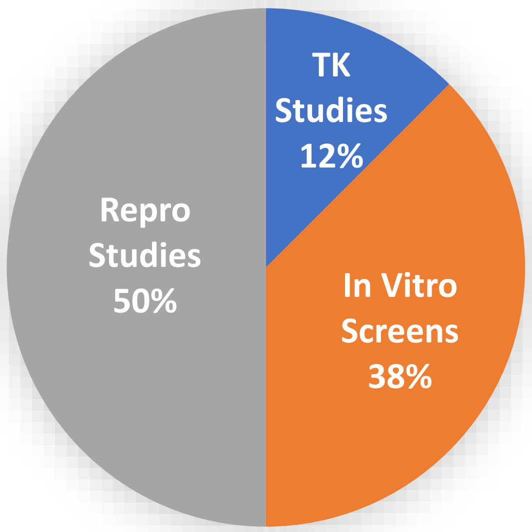
PFAS



IONIC LIQUIDS

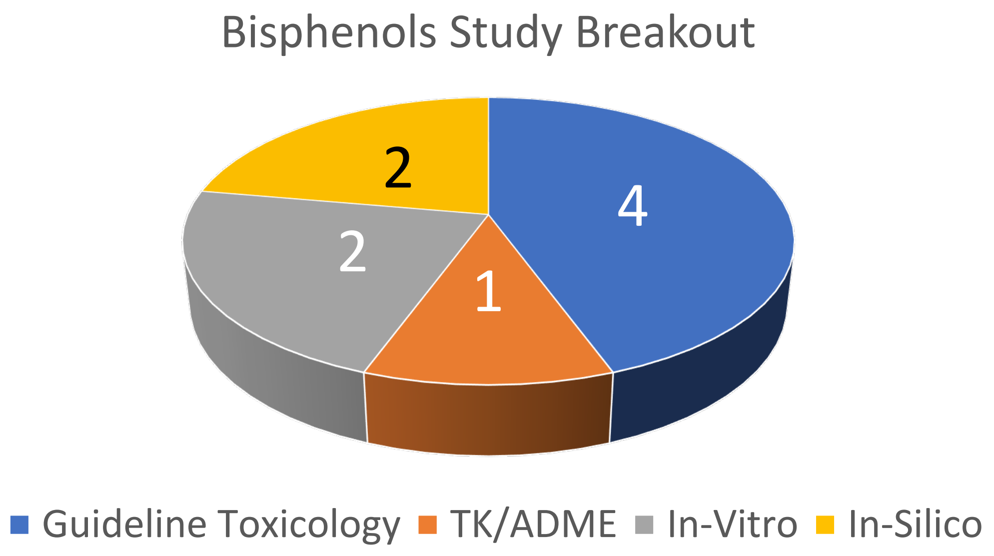


BISPHENOLS



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



- 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: Collaborate	Objective 2: Innovate	Objective 3: Evaluate
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?

Acknowledgements

DNTP Project Leads and Staff

EPA’s Safer Choice Program

EPA’s Office of Research and Development

Clean Production Action

Department of Defense

National Toxicology Program

Thank You!

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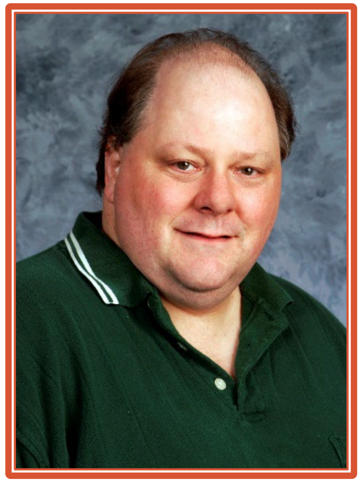

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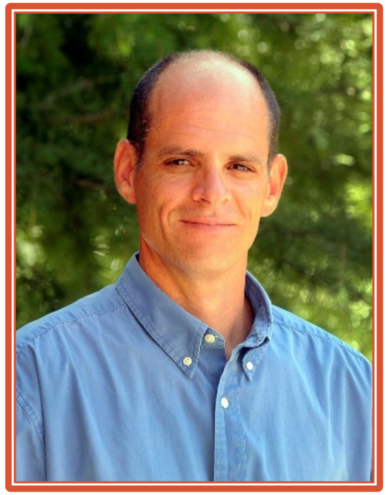

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Abbreviations and Acronyms

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