Safe and Sustainable Alternatives Program

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Problem Statement

Hazardous substances are often replaced by new or existing substances due to either discretionary (e.g., public pressure, economic consequences) or mandatory reasons (e.g., regulatory ban). When a chemical/substance is replaced, information about the replacement's potential to lead to effects that could pose similar or greater harm to human health than the original (i.e., regrettable substitutions) is often limited and not available in the public domain.

Objectives

The Safe and Sustainable Alternatives (SSA) program is structured around the following three objectives in collaboration with other Division of the National Toxicology Program (DNTP) program management teams:

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.
2. Identify and qualify effective tools and approaches through case studies that establish translational utility and refine proactive strategies for evaluation of alternative substances.
3. Evaluate the relative potential for human health effects with exposures to select alternative substances.

Rationale

Alternative chemicals and products are often purported to be better and safer than those they are replacing, yet there is often limited information in the public domain to identify the potential to cause adverse human health effects. To date, the regulatory bar for relative safety is low. Unfortunately, associations of environmental chemicals with human health effects are primarily identified retrospectively (e.g., perfluorooctanesulfonic acid (PFOS) has been associated with thyroid disruption, low birth weights, and cancer). Ideally, more proactive strategies would be a part of the solution. DNTP has a rich tradition of contributing high-quality study data to aid in addressing these public health challenges that include toxicology, ADME [absorption, distribution, metabolism, and excretion], computational modeling, and in vitro toxicology screening (e.g., Tox 21). However, these efforts often fall short in comparing the relative safety of alternatives for effective translation to human exposures. DNTP seeks to address the difficult questions that will empower proactive research on alternative substances. The aim is to ultimately reduce the toxicity burden of environmental chemicals through

focused advances in toxicology research. The SSA program seeks to reform the chemical-by-chemical approach and develop proactive strategies to reduce or eliminate these “whack-a-mole” cycles of regrettable substitutions via more efficient testing, expanded efforts to qualify and tune emerging toxicology tools and strategies, and expanded communication, coordination, collaboration through partnerships with the scientific community (e.g., industry, nonprofit, government, academic) to meet the contemporary challenges of environmental toxicology.

Public Health Context

A regrettable substitution is the replacement of a hazardous chemical with another similarly harmful, or in some cases more harmful, chemical. In the United States and worldwide, there have been many instances of regrettable substitutions. DDT [dichlorodiphenyltrichloroethane], an agricultural pesticide banned by the Stockholm Convention due to its biological persistence, bioaccumulation, and toxicity, was replaced by organophosphate pesticides, a group of chemicals that have shown both acute and chronic effects. Bisphenol-A, an endocrine-disrupting chemical used in consumer and industrial products, was replaced by the relatively data-poor alternatives bisphenol-S (BPS) and BPS, which ultimately revealed to be comparably efficacious endocrine-disruptors.

Regrettable substitutions promoted as better and safer are common in the field of environmental health sciences. Limited emphasis is placed on strategies and methods that proactively evaluate the potential for human health effects of alternatives (e.g., relative potencies, margins of exposure to biological and toxicological responses). This cyclic public health challenge is an opportunity to develop solutions that enable industry, regulators, and the public to find a better way forward.

Alignment with Mission, Goals, Strategic Pipeline

The SSA program is primarily oriented toward proactive and responsive research needs identified in partnership with external stakeholders. This program seeks to provide quantitative and actionable information with efficient and timely delivery. Building on DNTP's strong reputation of trusted science to support decision-making with existing products, the SSA program will promote green chemistry approaches and the identification of safer alternatives through innovative tools and tactics that leverage and shape all components of the translational toxicology pipeline. Facilitating the reduction of hazardous substances introduced into the marketplace through advances in environmental toxicology can help break the cycles of regrettable substitution and provide safer and sustainable alternatives.

The SSA program will use and refine the DNTP translational toxicology pipeline through case study investigations to shape our strategies for future evaluations. This includes computational and predictive tools (e.g., human ADME and toxicity), bioactivity screening, in vitro models, and in vivo studies that will improve understanding of the potential for adverse human health effects posed by data-poor chemicals and will inform stakeholder decision-making. Lastly, we will communicate with external stakeholders to identify gaps within existing safety evaluation strategies for chemical alternatives and areas of focus for DNTP.

Stakeholder Interest and Engagement

The objectives and activities of the SSA program intersect with those of multiple groups outside of DNTP, including existing partners that currently conduct chemical alternative assessments (e.g., European Chemicals Agency (ECHA), U.S. Environmental Protection Agency (EPA), GreenScreen). Additionally, there are many local, state, federal, and international agencies interested in or required to consider alternative materials without the requisite technical expertise or resources. The private sector, including individual corporations, industry advocacy groups and consultants, trade associations, and professional societies, seek enhanced information on suitable alternatives. Various external groups are working in the areas of product safety and sustainability, environmental impacts, and environmental justice. While these objectives overlap with other organizations, DNTP is uniquely positioned to address challenging gaps in these existing strategies. The SSA program will expand collaborative efforts with these organizations and further evolve emerging methodologies and strategies into translational approach methods.

Ongoing and Continuing Interactions

Stakeholder*	Issue and/or Project	Role of Stakeholder
ACS	ACS Green Chemistry Institute[1]	Customer
A4[2]	Advancing the science, practice, and policy of alternatives assessments and informed substitutions	Partner
ATSDR, CPSC, DoD, EPA, FDA, NCI, NIOSH	Federal interagency coordination on per- and polyfluoroalkyl substances (PFAS)-related research activities	Partners
DoD	Coordination principles to evaluate DoD procurement materials Aqueous film forming foams (AFFFs)	Partner; end user
ECHA	Strategy to promote substitution to safer chemicals through innovation[3] Bisphenols	Partner
Health Canada/University of Ottawa	Functional genomics approaches to relative characterization of PFAS	Collaborator
NIH	Sustainable Laboratory Practices Working Group[4] Green Labs Program[5] Sustainability Management Team[6]	Customer
OECD	Substitution and Alternatives Assessment Toolbox	Partner

[1] https://www.acs.org/content/acs/en/greenchemistry/about.html
[2] https://saferalternatives.org/
[3] https://echa.europa.eu/documents/10162/13630/250118_substitution_strategy_en.pdf/bce91d57-9dfc-2a46-4afd-5998dbb88500
[4] https://nems.nih.gov/green-teams/Pages/Sustainable-Laboratory-Practices-Working-Group.aspx
[5] https://nems.nih.gov/green-teams/Pages/NIH-Green-Labs-Program.aspx
[6] https://nems.nih.gov/green-teams/Pages/Sustainability-Management.aspx

Stakeholder*	Issue and/or Project	Role of Stakeholder
Society of Toxicology	Sustainable Chemicals through Contemporary Toxicology Specialty Section[7]	
University of Massachusetts Lowell Center for Sustainable Production	Founder and organizer of multiple green chemistry and alternatives assessment activities, e.g., the Chemical Footprint Project[8]	Partner
EPA Office of Research and Development	PFAS, AFFFs	Collaborator
EPA Office of Chemical Safety and Pollution Prevention	Safer Choice program[9]	Partner; end user

* A4 = Association for the Advancement of Alternatives Assessment; ACS = American Chemical Society; ATSDR = Agency for Toxic Substances and Disease Registry; CPSC = U.S. Consumer Product Safety Commission; DoD = U.S. Department of Defense; ECHA = European Chemicals Agency; EPA = U.S. Environmental Protection Agency; FDA = U.S. Food and Drug Administration; NCI = National Cancer Institute; NIH = National Institutes of Health; NIOSH = National Institute of Occupational Safety and Health; OECD = Organisation for Economic Co-operation and Development

Input Received

Our program introduction and engagement has already led to positive public and private feedback from leaders within the toxicology community. Moreover, we initiated interactions with the EPA Safer Choice program and, in coordination with the U.S. Department of Defense (DoD), we began interactions with the industry-based GreenScreen program to better identify strategies that characterize the toxicologic potential of safe and sustainable alternative chemicals. These interactions have revealed aspects of DNTP strategies that are exceeding the depth of toxicology evaluations (e.g., quantitative vs. qualitative) within external programs but that fall short of the breadth of effort needed for comprehensive toxicology research. Identifying the situations in which DNTP can advance the effectiveness and use of these efforts for human translation is a key gap for near-term action.

Milestones and Metrics

Measures of progress toward achieving the program objectives are outlined below. For each objective, individually aligned projects are listed along with relevant milestones. Milestones are grouped by expected timeframe as short-term (1 year), medium-term (2–3 years), and long-term (4–5 years) targets. All research objectives are expected to result in publicly available data housed in the CEBS [Chemical Effects in Biological Systems] database and in publications of key findings in the form of peer-reviewed manuscripts and National Toxicology Program (NTP) reports.

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.

To shape the path forward with actionable external communication and collaboration, the SSA program is working with external stakeholders to identify gaps within existing chemical alternatives' safety evaluation strategies as potential areas of focus for NTP. In consultation with various entities, we intend

[7] https://www.toxicology.org/groups/ss/SCCT/index.asp
[8] https://www.chemicalfootprint.org/
[9] https://www.epa.gov/saferchoice

to develop a chemical-agnostic strategy for approaching alternatives' assessments that includes data-poor scenarios.

Related activities: DoD, EPA PFAS collaboration, EPA Safer Choice

This is an emerging area of focus for DNTP that seeks to proactively break the cycle of regrettable substitutions in partnership with established and new external stakeholders. The SSA program has initiated new interactions with specific groups focused on safer alternatives, as summarized below, that would continue to evolve over time.

- Short-term:
  - Establish relationships with stakeholders; understand landscape.
  - Hold briefing with EPA Safer Choice program and planned briefings with the Organisation for Economic Co-operation and Development, EPA Office of Pollution Prevention and Toxics, California Environmental Protection Agency, industry groups, and nongovernmental organizations.
- Medium-term:
  - Identify key data and technology gaps wherein DNTP can contribute, including evaluating the utility of ADME-toxicokinetic (TK) information to guide prioritized decision-making and contextualization of hazard information.
  - Engage with sustainability initiatives within the National Institute of Environmental Health Sciences to identify opportunities for DNTP to contribute intellectually toward understanding hazardous chemicals.
- Long-term:
  - Provide a usable framework to advance the use of chemical alternatives prioritization and testing. This includes understanding the needs of our stakeholders and collaborating to develop a more effective prioritization schema/decision tree for action on data-poor chemicals.
  - Participate in Sustainable Chemistry Research and Development Act initiatives under the National Defense Authorization Act.
  - Explore the possibility of joining the Supercomputing for Safer Chemicals (SUPERSAFE) Consortium.

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.

The intention is to address specific toxicology research needs by extending current and emerging technologies into innovative toxicology evaluation strategies. The process aims to shape the evolution of the translational toxicology pipeline through iterative tuning of technologies and data integration into efficient, quantitative exemplar case study investigations for Next Generation Risk Assessments. These efforts would ideally reveal efficient action trees for identification of safer alternatives while simultaneously addressing contemporary toxicology challenges.

Related projects: Aqueous film forming foams (AFFFs) and per- and polyfluoroalkyl substances (PFAS).

Environmental pollution from PFAS is a preeminent challenge for modern toxicology research. A key driver of PFAS toxicity in humans appears to be their propensity for exceedingly long internal exposure half-lives. Enabling the scientific community to identify, reduce, and eliminate environmental chemicals that accumulate over time to biologically active concentrations is a primary goal of our PFAS research focus. Our research efforts include the estimation and integration of human ADME-TK estimates with

observed biological/toxicological response potencies to enable predictions such as "time to pathology" with an accumulating chemical using in vivo, in vitro, and computational model systems.

- Short-term:
  - Prepare summary report to DoD: AFFF in vitro transcriptomic screening (2021).
  - Design approach for prediction of PFAS hepatic bioaccumulation with human microphysiological systems (primary human hepatocytes, InSphero AkuraFlow).
- Medium-term:
  - Coordinate DNTP PFAS strategy (e.g., 120 chemicals with EPA Office of Research and Development Chemical Characterization and Exposure Division)
  - Prepare manuscript: AFFFs and constituents with in vitro liver transcriptomic screening (2021).
  - Prepare manuscript: Modeling the potencies PFAS toxicity (28-day exposures) using in vitro liver transcriptomic screening (2021).
  - Develop protocol for feasibility of in vitro estimates of PFAS hepatic bioaccumulation (2022).
  - Develop protocol and manuscript for evaluation of renal barrier function and transport.
- Long-term:
  - Qualify renal toxicity models for PFAS plasma bioaccumulation and toxicity.
  - Qualify human intestinal absorption model systems in collaboration with the Combined Exposures and Mixtures (CEM) program and the Novel Tools and Approaches program through case studies with PFAS and botanicals.
  - Encourage the evolution of computational and in vitro tools for safer alternatives (projects are needed).

Objective 3: Evaluate the relative potential for human health effects with exposures to select alternative substances.

This approach builds upon existing programmatic efforts related to regrettable substitutions (e.g., bisphenols and PFAS) to foster enhanced research designs with broader impact. Study designs leveraging multiple modules of the translational toxicology pipeline aim to expand the effectiveness of chemical 'safety' evaluations through hazard contextualization and translation. Study designs include:

- Concerted chemical set comparisons addressing plausible internal exposure scenarios;
- Mechanistic studies that reveal interpretable aspects of molecular and cellular responses to chemical exposures and their likelihood for human translation;
- In vitro studies with sufficient physiological relevance to model and infer potential for human toxicity and disease severity (e.g., mechanistic and pathological states, reversibility, tipping points); and
- Hypothesis-focused in vivo studies designed to address complex chemical-biological interactions and build confidence through data integration for human translation.

These studies would ultimately have the goal of identifying safer chemical alternatives while learning from past regrettable substitutions. The selected projects listed below reflect the scope of our active project inventory and our goals relative to completing each evaluation.

Related projects: AFFFs, bisphenols, and PFAS.

Environmental pollution from AFFF use by civilian and military firefighter organizations has led to environmental pollution with PFAS. It is essential to understand the relative potential for PFAS and other

structurally related chemicals to cause human toxicity with sufficient context to interpret the study findings and evolve approach methods for toxicology research. PFAS and PFAS mixtures have been identified as important case studies to expand our understanding of this class of chemicals while evolving the next generation of contextualized toxicology testing.

- Short-term:
  - Finalize the summary report for in vivo AFFF bioaccumulation, to be submitted to DoD in 2021
  - Finalize the bisphenol AF (BPAF) Modified One Generation (MOG) Developmental and Reproductive Toxicity report, to be issued in 2021
  - Complete the dermal sensitivity evaluation of four Ionic liquids, to be published in 2021
  - Complete the 3-month evaluation of four ionic liquids, study report to be issued in 2021
  - Complete the TK and ADME evaluation of BPAF in rats, to be published in 2021
- Medium-term:
  - Complete study of the developmental effects of 6,2-FTSA evaluation in 2022–2023
  - Complete the PFAS Responsive Evaluation and Assessment of Chemical Toxicity on 120 chemicals identified and available from EPA in 2022
  - Finalize the PFOA [perfluorooctanoic acid] PFOS dose-range finding (DRF) and MOG Rat and Mouse study report in 2022
- Long-term:
  - Conduct next-generation PFAS evaluation, including evaluating bioaccumulation potential in model systems (e.g., gut, renal, hepatic), hazard characterization, and mixtures absorption in partnership with the CEM program.
  - Publish bisphenol-S DRF/MOG (rat) and 2-week mouse study results in 2022; Toxicity report to be published by 2024.
  - Refine framework for integrated toxicology assessments across modules of the translational toxicology pipeline with additional case studies that include purported safer and less safe chemicals.

Value Proposition and Summary

The ultimate value of this program to DNTP will be realized by lowering the potential for adverse health outcomes by choosing safe and sustainable chemical alternatives. Most alternative chemicals introduced into the environment have limited or no information on human safety. Approaches that create actionable context for hazard characterization (e.g., internal exposure levels), in partnership with external stakeholders will be used to measure success and guide the evolution of program strategy. Given the emergence of state-of-the-art toxicology tools and human ADME-TK models, this program presents an opportunity to bridge translational gaps and enable more proactive toxicology research. Thus, DNTP is well-positioned to develop and qualify proactive strategies to assess the relative safety of alternatives that ultimately minimize the potential for regrettable substitutions and address a critical need for the toxicology research community.