

Consumer Products and Therapeutics Program

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Problem Statement

The large number of chemicals people are exposed to through the use of consumer products presents challenges for determining potential adverse human health outcomes. These challenges are unlikely to be met using the traditional, one-at-a-time testing regimen. There are no defined approaches that are sufficiently flexible or proven to address the myriad and mixtures of consumer products.

For therapeutics, unforeseen health effects may necessitate additional toxicity testing to address potential concerns, such as those that may present with individuals exposed to human immunodeficiency virus (HIV) therapies across the lifespan or during different life stages.

Objectives

The Consumer Products and Therapeutics (CPT) program is structured around the following three objectives:

1. Within the next 5 years, evaluate whether class-based methodologies are an effective framework for assessing potential human health effects of chemicals in consumer products by considering human, animal, and in vitro toxicity data. The evaluation includes the following sub-objectives for a chemical class of interest and uses a class-based assessment of organo-halogenated flame retardants (OFRs) as the exemplar to begin working the paradigm.
 - 1.1. Engage appropriate stakeholders (e.g., U.S. Consumer Product Safety Commission (CPSC), U.S. Food and Drug Administration (FDA) Center for Food Safety and Applied Nutrition (CFSAN)) in discussions regarding the selection and planning of class-based assessments.
 - 1.2. Identify key concerns associated with a chemical class (e.g., major adverse health effects at the lowest doses).
 - 1.3. Devise and implement a scoping plan to categorize available research to direct the class-based synthesis and identification of data-poor areas that limit evaluations.
 - 1.4. Examine available data generated by traditional and high-throughput new approach methodologies (NAMs) to predict, prioritize, and assess toxicity potential (e.g., Quantitative Structure-Activity Relationships (QSAR) and read-across, as well as empirical technologies such as in vitro assays and organ-on-a-chip).
 - 1.5. Assess the method's effectiveness at providing translatable health effects information across a chemical class.

2. Partner early with appropriate stakeholders (e.g., National Institutes of Health (NIH) Office of AIDS Research (OAR)) to provide impactful scientific knowledge on therapeutics.
 - 2.1. Support the NIH/OAR initiative to assess potential toxicities of combination antiretroviral therapies used for the treatment of HIV.
 - 2.2. Engage with stakeholders (e.g., FDA Center for Drug Evaluation and Research [CDER]) to share capabilities in toxicity evaluations unique to the Division of the National Toxicology Program (DNTP). Discuss cross-cutting issues of mutual interests wherein DNTP can provide impactful information.
 3. Strengthen and build new partnerships across federal agencies (e.g., NIH, U.S. Environmental Protection Agency (EPA), FDA, CPSC, National Institute for Occupational Safety and Health (NIOSH)) and nongovernmental organizations (NGOs) to contribute value-added research for the CPT program and to facilitate a broader dissemination of information to guide public health decisions.
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Rationale

Consumer products and therapeutics were combined to form the CPT program; however, given the differences in use, exposure, and regulatory structures between the two, the program management team (PMT) considers them separate categories to better address potential health effects.

Public Health Context

Chemical assessment of consumer products in the public health context is a two-fold challenge. The first challenge deals with the ubiquitous presence (e.g., frequent dermal, inhalation, and/or oral exposure) of these chemicals (some tested, some not) that are often in the form of mixtures/co-mixtures and that frequently result in low-level, chronic daily exposures. The second challenge is the relatively slow pace of the single-compound testing paradigm to gain knowledge and provide data for making informed decisions in the public health context. High-throughput NAMs capable of testing large numbers of chemicals aim to replace costly, time-consuming chemical-by-chemical methods. These approaches address multiple concerns, such as insufficient chemical data leading to false safety assumptions, known hazardous chemicals being substituted with untested compounds, and cumulative exposure and risk not being considered in one-chemical-at-a-time testing (e.g., OFRs). Class-based approaches expand the opportunities to use the breadth of available data for potentially addressing adverse effects of a larger number of chemicals.

For therapeutics, the CPT program has engaged key partners for discussions regarding compound evaluations or questions of mutual interest (e.g., discussions with FDA on PEGylated compounds, genotoxic impurities in drugs, characterization of nanomaterials). Presently, the primary focus for therapeutics research within DNTP is the evaluation of HIV therapies. OAR coordinates HIV and acquired immunodeficiency syndrome (AIDS) research across the NIH, and DNTP uses funds from OAR to address research questions associated with basic and translational research to understand potential comorbidities, coinfections, and complications associated with HIV combination antiretroviral therapies (ART). One of DNTP's overarching research priorities for therapeutics is to provide toxicity information to OAR stakeholders regarding potential issues faced by people with HIV (or people using HIV therapies prophylactically) across the lifespan or during different life stages. This research could help identify conditions associated with HIV-therapeutics toxicity and could provide stakeholders with information regarding potential issues requiring mitigation.

Alignment with Mission, Goals, Strategic Pipeline

The CPT program fully engages and aligns with DNTP's vision and mission. Evaluating potential toxicities that can lead to human health effects from exposure to the vast number of chemicals present in consumer products is a critical public health goal. The DNTP consumer products portfolio offers a unique opportunity to inform research and decision making by strategically directing our efforts toward class-based approaches. These class assessments require collaborative engagement across multiple scientific disciplines, and multidisciplinary team science is a core value at DNTP. For consumer products, the CPT program has started a chemical class assessment of OFRs as the exemplar of interest because of widespread human exposure and because of support from our CPSC stakeholder. DNTP has a strong history of research on flame retardants, as well as active projects at multiple levels of the pipeline, from in vitro and in vivo assays to a class-based cancer hazard assessment. Given the strength of developmental neurotoxicity data on flame retardants and mixtures-related exposure issues, which are common for consumer products, the CPT program is closely coordinating with the Developmental Neurotoxicity Health Effect Innovation program and the Combined Exposures and Mixtures program. The multidisciplinary class approach leverages DNTP capabilities across the pipeline, beginning with data mining/literature scoping to develop evidence maps. These maps will serve as a foundation for evidence-based decisions for analysis and downstream predictive toxicity testing by high-throughput methods that involve both in silico tools and in vitro model assays. This strategic approach to hazard testing has the potential to support, influence, and produce cutting-edge data that could impact public health decisions. Since the CPT program's aim for therapeutics is more focused, we are initiating communication with stakeholders to identify questions of interest. The collaborations across divisions of the National Institute of Environmental Health Sciences, stakeholders, and other programs are required to better address the complexity of public health challenges faced by the CPT program. Novel approach methods within DNTP, along with new communication channels with other programs, align with new DNTP directives and ensure collaborative and progressive translational toxicology instruction among current and future DNTP trainees.

Stakeholder Interest and Engagement

DNTP has provided hazard and toxicity data on single-compound assessments of chemicals in consumer products for over 40 years. Although DNTP planned and conducted research to examine toxicity across structurally related chemicals, it has not implemented a concerted effort at class-based assessment of consumer products. In order to strengthen DNTP's commitment to providing timely and trusted scientific information to inform public health decision making, the CPT program defined Objective 1 of this program as pursuing a class-based approach to assessment of chemicals in consumer products. The CPT program is committed to a transparent and collaborative process of stakeholder engagement as it begins this shift. Similarly, the CPT program is working closely with our partners, particularly FDA and NIH/OAR, to plan impactful DNTP therapeutics research focused on HIV/AIDS combination therapies, as well as considering other areas of mutual interest.

As stated in Objective 3, we will work to build and strengthen new partnerships across federal agencies (e.g., NIH, EPA, FDA, CPSC, NIOSH) and NGOs focused on CPTs. We will also seek active partnerships and input from stakeholders on the proposed phased approach for class-based consumer products testing methodologies. The CPT program is a new initiative that re-envision DNTP's consumer products testing as a strategic departure from single-chemical evaluations.

The PMT plans close communication with stakeholders in a phased approach over the next 5 years to evaluate whether class-based methodologies are an effective framework for assessing potential adverse effects of the multitude of chemicals in consumer products, secondary to low-level chronic exposures. The first phase of engagement focuses on primary stakeholders, including National Toxicology Program (NTP) partners (FDA and NIOSH) and key federal agencies (CPSC and EPA). As the program matures, engagement will expand to include additional agencies and outside groups to obtain broad input on key areas regarding research and class-based approaches.

As with consumer products, the first phase of outreach and communication for therapeutics focuses on primary stakeholders and groups that have a clinical interest in HIV combination therapeutics research (NIH/OAR and FDA).

Steps Taken to Engage Stakeholders

The CPT program is early in the process of engaging stakeholders to discuss its new objectives, and program members have begun working with key stakeholders on the first two of those objectives. For Objective 1, the program has partnered with CPSC on applying a class-based approach for a group of OFRs. CPSC commissioned a National Academies of Sciences, Engineering, and Medicine (NASEM) review, which recommended and outlined a class approach to testing subsets or subclasses of this large group of OFRs.¹ Subsequently, CPSC submitted a nomination to DNTP for scoping of OFRs health effects and exposure literature to support a class-based assessment. The CPT program is collaborating with CPSC to organize and advance the project. Similarly, we have been working with NIH/OAR clinical researchers on Objective 2 and will engage FDA on discussions over the proposed approach to therapeutics. Within the program, DNTP continues to engage stakeholders and subject matter experts on a project-specific basis for therapeutics and consumer products research. It is imperative the program directs its attention to strengthening communication and building upon existing and new partnerships with stakeholders that can provide added value (to both the program and stakeholders), leveraging experience in the field as we shift our focus to class-based approaches. Implementation of innovative testing methods, such as class-based approaches, for critical CPT research areas can facilitate a broader dissemination of information to guide public health decisions.

Ongoing and Continuing Interactions

Stakeholder	Issue	Role of Stakeholder
California Environmental Protection Agency	Consumer products: Chemicals in personal care products	User; advisor for personal care product assessments
Centers for Disease Control and Prevention	Consumer products: Chemicals in personal care products	Advisor for personal care product assessments
National Institute for Occupational Health and Safety	Consumer products: Chemicals in personal care products	Partner; advisor for personal care product assessments
U.S. Consumer Product Safety Commission	Consumer products: Identifying critical research, uncertainties for class-based evaluations	Partner; collaborator on OFR class approach

¹ National Academies of Sciences, Engineering, and Medicine. (2019) A Class Approach to Hazard Assessment of Organohalogen Flame Retardants. Washington, D.C.: The National Academies Press.
<https://doi.org/10.17226/25412>.

Stakeholder	Issue	Role of Stakeholder
U.S. Food and Drug Administration	Therapeutics: Determine whether there are any additional HIV/AIDS-specific compound issues; consider projects of mutual concern	Partner
National Institutes of Health, Office of AIDS Research	Therapeutics: Long-term toxicity assessments of HIV combination antiretroviral therapies	Advisor
U.S. Environmental Protection Agency	Consumer products: Identifying critical research, uncertainties for class-based evaluations	Partner; potential collaborator

Input Received

Stakeholder input to date has been supportive of the class-based approach for assessing chemicals in consumer products as a method to develop more timely health and toxicity data focused on human relevance that addresses a more extensive chemical space. Opportunities for input into this process will be provided at the NTP Board of Scientific Counselors (BSC) meetings, topic-focused workshops or symposia, and through public engagement. The CPT program is early in the process and there is a need to work closely with stakeholders to identify and target impactful areas of consumer product research and critical research needs. The strong support from CPSC for addressing OFRs as the first exemplar for a class-based approach builds on DNTP experience with these chemicals and the proposed class approach outlined by the 2019 NASEM report. We have also received consistent positive feedback and support for DNTP assessment of chemicals in personal care products. The integration of experimental animal studies with epidemiological data is a recognized challenge for personal care products because animal data stem largely from single chemical exposure studies, whereas human exposure may be limited to product use categories or reflect combined chemical exposure and mixtures.

As this program refines the DNTP focus on therapeutics, we are working closely with FDA to address concerns that projects in Objective 2 could overlap with, or be redundant to, FDA plans and activities. We will continue to communicate early and often with FDA to harmonize efforts. Given the strong support for research on HIV/AIDS therapeutics from NIH/OAR, collaborative efforts will continue.

Milestones and Metrics

A roadmap with milestones and measures of progress for achieving CPT program objectives is outlined below. Milestones are organized into short-term (1 year), medium-term (2–3 years), and long-term (4–5 years) targets. All project and final objectives are expected to result in publicly available data housed in the DNTP Chemical Effects in Biological Systems database and in publication of key findings in NTP reports or peer-reviewed manuscripts.

Objective 1: Within the next 5 years, evaluate whether class-based methodologies are an effective framework for assessing potential human health effects of chemicals in consumer products by considering human, animal, and in vitro toxicity data. The evaluation includes the following sub-objectives for a chemical class of interest and uses a class-based assessment of OFRs as the exemplar to begin working the paradigm.

- 1.1 Engage appropriate stakeholders (e.g., CPSC, FDA CFSAN) in discussions regarding the selection and planning of class-based assessments.

- 1.2 Identify key concerns associated with a chemical class (e.g., major adverse health effects at the lowest doses).
- 1.3 Devise and implement a scoping plan to categorize available research to direct the class-based synthesis and identification of data-poor areas that limit evaluations.
- 1.4 Examine available data generated by traditional and high-throughput NAMs to predict, prioritize, and assess toxicity potential (e.g., QSAR and read-across, as well as empirical technologies such as in vitro assays and organ-on-a-chip).
- 1.5 Assess the method's effectiveness at providing translatable health effects information across a chemical class.

Key Projects: OFR class-approach assessment

This project seeks to establish and conduct assessments of potential human health effects of chemicals in consumer products using class-based methodologies.

- Short-term:
 - Establish first exemplar class approach (OFRs; CPSC partner).
 - Establish work assignment and project plan and complete internal review steps.
 - Begin literature searching, screening, and mapping of health effects and exposure evidence on 2–3 classes.
- Medium-term:
 - Publish OFR evidence maps and use for decision making. Critical tasks include (1) identifying target toxicity and chemical space for application of class approach in analysis or further research, and (2) using the evidence map to inform decisions that drive next steps in predicting OFR toxicity (e.g., DNTP high-throughput testing methods) directed at data gaps and reducing uncertainty.
 - Collaborate with stakeholders and combine inputs on potential additional class-approach projects to assess chemicals in consumer products.
- Long-term:
 - Explore the potential for targeted data generation with high-throughput methods to expand the application of class approach.
 - Assess the effectiveness of the class-approach analysis for flame retardants and other class-approach projects at providing translatable health effects information.

Objective 2: Partner early with appropriate stakeholders (e.g., NIH/OAR) to provide impactful scientific knowledge on therapeutics.

- 2.1 Support the NIH/OAR initiative to assess potential toxicities of combination antiretroviral therapies used for the treatment of HIV.
- 2.2 Engage with stakeholders (e.g., FDA CDER) to share capabilities in toxicity evaluations unique to DNTP. Discuss cross-cutting issues of mutual interests wherein DNTP can provide impactful information.

Key Projects: HIV therapeutics (multiple combination studies)

These studies address unforeseen research needs on health effects of HIV therapeutics secondary to lifetime and different life stage exposures identified by NIH/OAR and clinicians.

- Short-term:
 - Continue communications with OAR stakeholders for ongoing and proposed combination therapy studies, as applicable.
 - Continue communications with FDA partners on issues of mutual concern.

- Medium-term:
 - Complete and report present studies on combination therapies; work with stakeholders on communication strategies to disseminate information to clinicians.
 - Conduct cardiovascular and neurological evaluations in a combined in vivo and in vitro assay approach to address chronic/lifetime HIV combination therapeutics exposure.
 - Building from these studies, discuss interest from stakeholders to leverage DNTP capabilities to identify potential novel alternative or high-throughput approaches (in silico and in vitro) for more rapid assessment.
 - Expand communications with present and future stakeholders on therapeutics issues of mutual concern, including issues related to specific HIV therapies (e.g., new or additional therapies) and other emerging issues (e.g., diversity of responses).
- Long-term:
 - Address upcoming issues of concern and potentially assess the effectiveness of high-throughput approaches for HIV therapies.
 - Conduct follow-up discussions with the FDA on select areas of mutual interest.

Objective 3: Strengthen and build new partnerships across federal agencies (e.g., NIH, EPA, FDA, CPSC, NIOSH) and NGOs to contribute value-added research for the CPT program and to facilitate a broader dissemination of information to guide public health decisions.

Key Projects: Continued engagement with CPSC, FDA, and OAR

- Short-term:
 - Outreach to initial stakeholders (CPSC, FDA, NIOSH, EPA).
 - Seek ideas and find mutual agreement among areas of concern that align with Objectives 1 and 2 of the program.
 - Seek input from the BSC on the overarching program plan.
- Medium-term:
 - Expand engagement to other federal and international stakeholder agencies.
 - Familiarize NGOs with the program objectives.
 - Encourage outreach to the program on areas of common interest and future interaction and explore partnerships with NGOs.
 - Plan workshops to share program objectives and initial projects and to obtain feedback from stakeholder community.
- Long-term:
 - Devise an approved plan of action for outreach on future specific projects, if identified stakeholders have not already expressed interest.
 - Attend and/or plan a symposium, meeting, or workshop with engaged stakeholders to share advancements made by the program in the areas of consumer products (e.g., class-based OFR testing) and therapeutics (e.g., HIV combination therapeutics).

Value Proposition and Summary

DNTP maintains a defining leadership role in advancing toxicology and is uniquely situated to evaluate CPTs for potential human health effects by leveraging its partnerships, resources, competencies, and past CPT experience. Investigation of a class-analysis testing approach by this program for consumer products streamlines testing and serves to redefine individualized examination of select chemicals. This strategic approach to hazard testing has the potential to support, influence, and produce cutting-edge data that could impact public health decisions. Knowledge gathered by this higher throughput approach

minimizes result timelines and (by batch processing) reduces costs while providing value-added data on more chemicals of potential concern. Partnerships with the FDA and NIH/OAR serve the clinical community by targeting toxicity research to address concerns and providing relevant data to support decisions on the use of HIV combination therapies over a lifespan and during different life stages. Partnering with therapeutic regulatory agencies helps to define the research areas of mutual concern and supports clinicians and the public with data to inform treatment decisions. DNTP's immense experience with stakeholders on establishing valued communications and building rewarding partnerships with governmental, nongovernmental, and international agencies serves to direct attention toward critical CPT research areas and to facilitate broader dissemination of information to guide public health decisions. Integration of DNTP resources and expertise, along with state-of-the-art advancements in toxicology and partnerships with engaged stakeholders, fortifies these areas and provides expertise to the public and health care workers to support improved public health.