

Modernizing the Process and Bringing Innovative Science to Evaluate New Chemicals Under TSCA

Problem Statement, Vision and Research Action Plan for Public Comment

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Background

On June 22, 2016, the Toxic Substances Control Act (TSCA) was amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act.¹ The EPA Office of Pollution Prevention and Toxics (OPPT) is responsible for carrying out the mandates of TSCA, which include provisions for regulating both existing and new chemicals. For new chemicals, OPPT's New Chemicals Division (NCD) is responsible for their review prior to introduction into U.S. commerce (via either import or domestic manufacturing). NCD has received an average of 500 applications (more properly called notices) per year since 2010 and a total of over 50,000 since 1979. The evaluation process is posted on the EPA website.² Depending on the type of notice, the statute/regulations generally require EPA to make decisions within 30 or 90 days of receipt.

OPPT is proposing to develop and implement a multi-year collaborative research program to modernize the process and bring innovative science to the review of new chemicals under TSCA before they can enter the marketplace. This effort will be performed in partnership with the Agency's Office of Research and Development (ORD) and other federal institutions (*e.g.*, the Division of the National Toxicology Program [DNTP] at the National Institute of Environmental Health Sciences [NIEHS] in the National Institute of Health [NIH]) to leverage the expertise and resources of these entities to address TSCA-specific needs as well as to enhance broad applicability of the research. The results of the effort are expected to increase the efficiency of the process, but more importantly bring innovative science to TSCA new chemicals human health and ecological risk assessments, and decisions for protecting human health and the environment using the authority under TSCA Section 5.

Many new chemicals have little to no chemical-specific information available for assessment. To address this long-standing information limitation, OPPT has led the world in the use of Quantitative Structure-Activity Relationships (QSARs) and other predictive models coupled with the use of category-based approaches to evaluate human and environmental hazards and exposures.³ The methods, approaches, and tools developed over the past four decades have been used successfully to carry out evaluations under TSCA since 1979.⁴

Prior to the 2016 Lautenberg amendments, the regulatory outcomes for new chemicals were to: drop from further review (*i.e.*, allow for introduction into commerce without regulation); regulate pending development of information (including any required testing prior to commercial manufacture); or regulate based on whether the new chemical or new use "will present" an unreasonable risk finding. The 2016 Lautenberg amendments introduced several new provisions that impact the regulatory outcomes for new chemicals. For example, EPA must now make an affirmative finding regarding safety for each new chemical or significant new use of a chemical (identified by EPA in rulemaking), and that finding determines whether and how EPA regulates the new chemical. The statute sets forth five possible determinations: (1) The chemical or significant new use presents an unreasonable risk of injury to human health or the environment; (2) Available information is insufficient to allow the Agency to make a reasoned evaluation of the health and environmental effects associated with the chemical or significant new use; (3) In the absence of sufficient information, the chemical or significant new use may present an unreasonable risk of injury to health or the environment; (4) The chemical is or will be produced in substantial quantities and either enter or may enter the environment in substantial quantities or there is or may be significant or substantial exposure to the chemical; or, (5) The chemical or

¹ Go to: [2016 amendments to TSCA](#).

² Go to: [Reviewing New Chemicals under TSCA](#)

³ Go to: [Predictive Models and Tools for Assessing Chemicals under TSCA](#)

⁴ Although TSCA was passed in 1976, the first premanufacture notice (PMN) was not received until 1979.

significant new use is not likely to present an unreasonable risk of injury to human health or the environment.⁵ These changes in the law require a full assessment for *all* cases (*i.e.*, no cases are dropped from further review).

These new requirements provide an opportunity to update and refine existing tools and methods and incorporate additional new approach methodologies (NAMs⁶) while enhancing transparency and modernizing the human health and ecological risk assessment process for new chemicals. The shift in approaches may confer added benefits such as addressing additional hazard data gaps and/or furnishing more information for making affirmative safety findings.

Another important aspect of the 2016 amendments to TSCA is the addition of a new subsection to the law, Section 4(h) entitled *Reduction of Testing in Vertebrates*. The law requires that "... (T)he Administrator shall reduce and replace, to the extent practicable, scientifically justified, and consistent with the policies of this title, the use of vertebrate animals in the testing of chemical substances or mixtures under this title..." (4(h)(1)). This subsection further states that before EPA can request or require testing in vertebrate animals, reasonably available existing information must be considered, including toxicity information, computational toxicology and bioinformatics, and high-throughput screening methods and prediction tools (Section 4(h)(1)(A)).⁷ As required in Section 4(h)(2)(A), OPPT released its Strategic Plan in 2018 to promote the development and implementation of alternative test methods and strategies.⁸ The NRC 2007 report on *Toxicity Testing in the 21st Century: A Vision and a Strategy*⁹ recognizes the implausibility that *in vivo* testing in vertebrate animals can be done on the thousands of chemicals in commerce. OPPT has long used predictive models and other non-vertebrate methods for evaluating new chemical submissions. As suggested in Section 4(h), new chemical reviews need to continue to incorporate new, innovative methods, approaches and tools in order to maintain a modern and efficient process.

TSCA requires OPPT to protect against disclosure of TSCA Confidential Business Information (CBI) where that information is eligible for protection. Historically, the development of human health and ecological risk assessments for new chemicals has relied heavily on information and limited data provided in a new chemical submission with CBI claims associated with it. The reliance on TSCA CBI data for new chemical evaluations reduces transparency and therefore the public's confidence in EPA's decisions. Efforts have been underway since the 2016 amendments to TSCA to make information claimed TSCA CBI information publicly available where the information is not entitled to confidential treatment.¹⁰

Finally, OPPT's TSCA chemical information management system needs to be modernized to increase transparency and efficiency in the decision-making process. EPA does not currently have a computing infrastructure to support the different types of data and information it receives and uses for reviews under its TSCA authorities. EPA has been working to modernize its chemical information system that supports the entirety of the TSCA program. Although the systems modernization effort is a separate endeavor, it is necessary for full implementation of the tools developed under this research proposal. This initiative contributes to a long-

⁵ Section 2604 (a)(3) at [15 USC Chapter 53](#)

⁶ As stated in the [TSCA Strategic Plan](#), new approach methodologies, or NAMs, "...has been adopted as a broadly descriptive reference to any technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment that avoids the use of intact animals." (p.6).

⁷ Section 4(h)(1)(B) contains further considerations, including encouraging and facilitating: "... (i) the use of scientifically valid test methods and strategies that reduce or replace the use of vertebrate animals while providing information of equivalent or better scientific quality and relevance that will support regulatory decisions under this title; (ii) the grouping of 2 or more chemical substances into scientifically appropriate categories....and (iii) the formation of industry consortia to jointly conduct testing to avoid unnecessary duplication of tests..."

⁸ Go to: [Strategic Plan](#). The law uses the phrase "alternative test methods and strategies", which is considered synonymous to the phrase New Approach Methodologies, or NAMs.

⁹ <http://dx.doi.org/10.17226/11970>

¹⁰ Go to: <https://www.epa.gov/tsca-cbi/epa-review-and-determination-cbi-claims-under-tsca>

term goal of using information that is interoperable with the International Uniform Chemical Information Database (IUCLID).¹¹

This document provides a high-level overview of a multi-year research plan focused on modernizing the process and innovating the science used in new chemical evaluations under TSCA. This includes methods, approaches, and tools used for TSCA new chemicals risk assessments. This plan is being released for public comment, and a more detailed plan will be presented to the ORD Board of Scientific Counselors (BOSC) later in the calendar year. While the focus of the current plan is on the first five years, we expect that modernization of data management in OPPT will complement the research effort and extend beyond these initial five years.

Problem and Vision Statements

Prior to developing this research plan, OPPT developed a problem formulation statement.

PROBLEM STATEMENT:

Using the best available science involves OPPT's use of methods, approaches, and tools to evaluate new chemicals prior to their entrance into US commerce, and refining and updating them where appropriate. Any changes should align with statutory deadlines, be operational in a data poor environment, make effective use of new data sources and approaches, and be transparent to the extent practicable given that TSCA CBI may be used in the development of these approaches.

The following vision statement provides the foundational concepts that need to be included in the research to address the problem statement.

VISION STATEMENT:

Continue to evolve OPPT's use of new and existing methods, approaches, and tools for evaluating new chemicals under TSCA that typically lack specific information (*i.e.*, are data poor) on human health and environmental risks through the use of innovative science.

Proposed Multi-Year Research Plan

An integrated research program is being proposed to address the problem statement and achieve the vision outlined above. This program will involve extensive collaboration across various EPA programs, federal agencies, and external stakeholders.

OPPT is collaborating closely with ORD's Center for Computational Toxicology and Exposure (CCTE) and Center for Public Health and Environmental Assessment (CPHEA), to develop and implement this research plan. Additionally, internal and external partners critical to delivery of the research plan will be consulted for input and research contributions.

The proposed research is focused on five areas described below and summarized in Table 1. Some activities are already underway while others are new and have not yet started.

¹¹ See <https://iuclid6.echa.europa.eu/project-iuclid-6>

1. Update and Refine Chemical Categories

As TSCA new chemical notices are typically data poor, OPPT has historically relied heavily on the use of chemical categories¹² and read-across¹³ as methods to fill data gaps, particularly for hazard characterization. OPPT currently uses the 2010 version of the New Chemical Category Document which identifies 56 chemical categories.¹⁴ When OPPT evaluates a new chemical, determining if it belongs in an existing category is important for evaluating human health or environmental effects. This allows information available on members of the category to be used to “read-across” to the new chemical.

Rather than refining the existing categories – or adding new ones – to the 2010 document, OPPT is proposing to develop a systematic, transparent, and reproducible approach for modernizing both chemical categories and read-across methods. OPPT will work with ORD researchers and other collaborators to identify scientific information to support chemical categories and read-across methods, such as: structural (and other) boundaries; physical-chemical properties; structural alerts for hazard, fate, exposure, and/or functional uses; mechanistic and toxicokinetic data from NAMs; and/or, existing hazard data. The new approach will document the data used to inform chemical categories as well as the basis of any similarity or read-across applications in a systematic manner.

The proposed approach will increase the efficiency of new chemical reviews and promote the use of the best available data to protect human health and the environment.

2. Develop and Expand Databases Containing TSCA Chemical Information

In addition to the information submitted for a new chemical, information on other TSCA chemicals may be found in a wide variety of public sources¹⁵ as well as in legacy OPPT TSCA CBI files. However, many of the public sources as well as the TSCA CBI data are not in a digital form that can be efficiently searched, analyzed, and used to develop and refine QSAR models, inform the refinement and development of chemical categories, and provide critical data for analogs in read-across evaluations of new chemicals.

OPPT and ORD are proposing to continue expanding existing ORD databases and curation¹⁶ efforts on physical-chemical properties (ChemProp), environmental fate (ChemProp)¹⁷, chemical functional use (CPDat¹⁸), multimedia monitoring data (MMDB¹⁹), ecological hazard (ECOTOX²⁰), human health hazard (ToxVal²¹, ToxRefDB²²), and toxicokinetics (CvT²³, Httk²⁴). The information in the ORD

¹² Section 26(c) of TSCA allows EPA to take action with respect to a category of chemical substances, which is defined in part as “a group of chemical substances the members of which are similar in molecular structure, in physical, chemical, or biological properties, in use, or in mode of entrance into the human body or into the environment, or the members of which are in some other way suitable for classification as such for purposes of [TSCA.]” The Organization for Economic Cooperation and Development (OECD) defines a category as “(C)hemicals whose physical-chemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or ‘category’...” (p.11 in OECD, 2017).

¹³ Read-across is defined as a data gap filling technique that relies on an analog or category approach, with analogs or categories defined on the basis of similarity of structure, properties, or other information. To “read-across” is to apply data from a tested chemical for a particular property or effect to similar untested chemicals. See

<https://dx.doi.org/10.14573/altex.1410071> and <https://dx.doi.org/10.1016/j.yrtph.2016.05.008> for further discussion.

¹⁴ See [Chemical Categories Used to Review New Chemicals under TSCA](#)

¹⁵ Examples include: [EPA/ORD CompTox Dashboard](#), [eChemPortal](#), [OPPT Chemview](#)

¹⁶ This would include checking for data accuracy, adequacy, acceptability and appropriate documentation of all information.

¹⁷ <https://doi.org/10.1016/j.comtox.2019.100096>; <https://doi.org/10.1186/s13321-017-0247-6>

¹⁸ <https://doi.org/10.1038/sdata.2018.125>

¹⁹ Isaacs KK *et al.* (submitted). A Harmonized Chemical Monitoring Database for Support of Exposure Assessments.

²⁰ <https://cfpub.epa.gov/ecotox/>

²¹ <https://doi.org/10.1186/s13321-017-0247-6>

²² [10.1016/j.reprotox.2019.07.012](https://doi.org/10.1016/j.reprotox.2019.07.012)

²³ [10.1038/s41597-020-0455-1](https://doi.org/10.1038/s41597-020-0455-1)

²⁴ <https://cran.r-project.org/web/packages/httk/index.html>

databases will be mapped to standardized reporting templates, stored in IUCLID as appropriate and will be publicly available. Literature mining tools for information retrieval and extraction will also be refined and further developed to rapidly screen the open and gray literature for relevant information on chemicals and associated analogs, with publication of the tools and approaches employed.

In addition, OPPT will plan to identify, extract, curate and catalog available CBI data on chemistry, hazard, fate, and exposure from different TSCA CBI databases and information. This will include digitizing existing physical records (largely paper and some microfiche) to capture all relevant CBI information for a given chemical substance. Available TSCA CBI information will be combined with publicly available sources, such as information from ORD databases, to expand the amount of information available, thereby enhancing chemical reviews and enabling efficient sharing of chemical information across EPA. Safeguards for CBI will be maintained as appropriate in this process. This initiative to digitize while protecting TSCA CBI contributes to a long-term goal of maintaining and utilizing fully computationally accessible data within OPPT. Based on the size of this task, ongoing work to achieve this may extend beyond the initial collaborative research plan described here.

The proposed effort will result in EPA having modern relational databases containing TSCA-relevant physical-chemical properties, environmental fate/transport, hazard, and exposure information to ensure the efficient searching of existing chemical information. It will further expand chemical information for developing chemical categories, QSAR, and other predictive models and will enable efficient sharing of chemical information within EPA.

3. Develop and Refine QSAR and Predictive Models for Physical-Chemical Properties, Environmental Fate/Transport, Hazard, Exposure, and Toxicokinetics

OPPT has developed and applied a large suite of QSAR and other predictive models to estimate physical-chemical properties, exposure, environmental fate/transport, and hazard.²⁵ OPPT and ORD are proposing to update and/or improve existing OPPT QSAR and predictive models and enable regular model updates. The data used to develop and update QSAR and predictive models will be derived from the curated public and TSCA CBI databases described above in Research Area #2. Experts from OPPT will work with ORD colleagues to evaluate all appropriate models, including evaluation of the data used to build models and model performance against measured data, to ultimately determine the best suite of models for use by OPPT for regulatory purposes.²⁶ This will include working with other stakeholders and peer reviewers to build confidence that the models meet the TSCA statutory requirement of Section 4(h)(1)(B) to develop... “i) the use of scientifically valid test methods and strategies that reduce or replace the use of vertebrate animals while providing information of equivalent or better scientific quality and relevance that will support regulatory decisions ...” The need to generate additional data may be identified, and this is addressed in Research Area #4.

The goal of this effort is to update the models to reflect the best available science, increase transparency, and establish a process for updating these models as science allows. This will enhance the capabilities of OPPT to perform risk assessments for new chemicals. In addition, refining and developing such tools will lead to their use by EPA, submitters, and other stakeholders in designing safer chemicals, and will build confidence in their use for regulatory purposes.

²⁵ [Predictive Models and Tools for Assessing Chemicals under TSCA](#)

²⁶ Using the OECD principles for validating QSAR models (see [OECD 2007](#))

4. Explore Ways to Integrate and Apply NAMs in New Chemical Assessments

Section 4(h) of TSCA promotes reducing testing on vertebrate animals and sets forth requirements for such testing. As recognized in OPPT's Strategic Plan,²⁷ leveraging *in vitro* NAMs to generate mechanistic, hazard, and toxicokinetic data may further inform data gap filling approaches for new chemicals. As required under TSCA 4(h), OPPT maintains a list of NAMs that are scientifically reliable, relevant, and capable of providing information of equivalent or better scientific reliability and quality to that which would be obtained from vertebrate testing.²⁸

EPA and the broader scientific community have invested heavily in the development of *in vitro* NAMs. As part of this multi-year research plan, OPPT is proposing to take advantage of previous and ongoing research that has identified important biological targets representing potential hazards, increased the predictivity of *in vitro*-to-*in vivo* extrapolation (IVIVE) of dose, and continues to develop cost effective technologies that broadly characterize biological activities across pathways, processes, and different cell types. OPPT will work with ORD and other federal partners to develop, evaluate, and apply *in vitro* NAMs for: 1) collecting mechanistic, hazard, and toxicokinetic data on new chemicals submitted to OPPT; 2) developing and updating QSARs for predicting key hazards; and 3) informing the development and refining of chemical categories for read across.

The *in vitro* NAMs will be evaluated for reliability and relevance for new chemical evaluation. Fit-for-purpose application of NAMs will rely, to the extent possible, on the concepts of (1) adverse outcome pathways (AOPs) and the key events leading to toxicity; and (2) Integrated Approaches to Testing and Assessment (IATA) for weight of evidence evaluation and the use of Defined Approaches (DAs).²⁹ Although some informative NAMs may not be associated with an IATA or DA and some health outcomes do not have established AOPs, this does not prevent OPPT from applying these methods if they represent best available science.

The proposed effort is intended to develop a suite of accepted, fit-for-purpose NAMs that could be used by external stakeholders for testing and data submissions under TSCA as well as informing and expanding new chemical categories.

5. Develop a TSCA New Chemicals Decision Support Tool to Modernize the Process

Within OPPT, searching, collating, and integrating data on new chemicals is inefficient and hinders the timeliness of making decisions under TSCA timelines. The international regulatory community has been moving towards using IUCLID to capture, store, maintain and exchange data on intrinsic and hazard properties of chemical substances. Data in IUCLID are centered around standardized reporting templates consistent with internationally accepted test guidelines. ORD is proposing to use IUCLID to capture, store and maintain publicly available data on intrinsic and hazard properties and exposure related data of chemicals. These efforts will promote data interoperability between OPPT, ORD, and other stakeholders.

Available digitized data for TSCA chemicals is critical for delivery of a decision support tool that *integrates* the various information streams specifically for evaluation of chemical risks to human health and the environment in a timely and transparent manner. OPPT and ORD propose to collaborate on

²⁷ See published plans by [OPPT under TSCA \(2018\)](#) and by [EPA](#) for the Agency (2021).

²⁸ See [TSCA Section 4\(h\) NAM list](#)

²⁹ AOP; see G Patlewicz et al. (2015). Proposing a scientific confidence framework to help support the application of adverse outcome pathways for regulatory purposes. *Regul Toxicol Pharmacol.* 71(3):463-77. doi: 10.1016/j.yrtph.2015.02.01. IATA - see [IATA and Defined Approaches \(OECD 2017\)](#).

identifying the appropriate content and workflow associated with the tool. For example, the proposed tool may allow expert chemists to examine the structure of each new substance(s) or groups of related compounds in a mixture. It is further envisioned that information on chemical categories and estimates of physical chemical properties, environmental fate, hazard, and toxicokinetics generated from predictive and *in vitro* models will be automatically presented in the tool thereby limiting the manual searching, compiling, and analysis that was required previously.

The decision support tool will more efficiently integrate all the data streams (e.g., chemistry, fate, exposures, hazards) into a final risk assessment and transparently document the decisions and assumptions made. This will facilitate the new chemicals program tracking decisions over time and evaluating consistency within and across chemistries.

Table 1. Summary of the Five Research Areas in the Multi-Year Research Plan

	Research Area	Problem	Approach	Expected Outcome(s)
1	Update and Refine Chemical Categories	Currently 56 TSCA categories, last updated 2010	Systematically define chemical categories and analogues for read-across using structural (and other) boundaries; physical-chemical properties; structural alerts for hazard, fate, exposure, and/or functional uses; existing hazard data; and/or, <i>in vitro</i> mechanistic and toxicokinetic data from NAMs	This will increase the efficiency of new chemical reviews and promote the use of the best available data to protect human health and the environment.
2	Develop and Expand Databases Containing TSCA Chemical Information	Existing TSCA information is not computationally accessible or easily searchable	<p>Extract and curate available TSCA CBI study information</p> <p>Continue extraction and curation of physical-chemical property, environmental fate, hazard, and exposure information (non-CBI) in ORD databases</p> <p>Map information in ORD databases to standardized reporting templates and store in an International Uniform Chemical Information Database (IUCLID)</p>	The TSCA CBI information will be combined with publicly available sources to expand the amount of information available, enhancing chemical reviews and enabling efficient sharing of chemical information across EPA. Safeguards for CBI will be maintained as appropriate in this process.

	Research Area	Problem	Approach	Expected Outcome(s)
3	Develop and Refine QSAR and Predictive Models for Physical-Chemical Properties, Environmental Fate/Transport, Hazard, Exposure, and Toxicokinetics	Currently used models are not always publicly accessible, easy to update with additional chemicals, or the best performing for all chemistries	Develop and update QSAR and predictive models using existing data and curated data from Research Area #2 Evaluate models to determine the best suite for use by OPPT for regulatory purposes	Updated models that reflect the best available science, increased transparency, and a process for updating these models as science allows.
4	Explore Ways to Integrate and Apply NAMs in New Chemical Assessments	Reduction in the use of vertebrate animals in accordance with TSCA Section 4(h) Many PMN submissions are data poor Amended TSCA requires affirmative determination regarding unreasonable risk	Develop and evaluate a suite of <i>in vitro</i> NAMs for informing new chemical evaluations Use mechanistic and toxicokinetic <i>in vitro</i> NAMs to inform and refine chemical categories in Research Area #1	A suite of NAMs that could be used by external stakeholders for testing and data submissions under TSCA as well as informing and expanding new chemical categories
5	Develop a TSCA New Chemicals Decision Support Tool to Modernize the Process	Searching, collating, and integrating data for new chemical assessments is inefficient and costly	Build proof of concept software workflow that integrates all data streams in a new chemical risk decision context	A decision support tool that will efficiently integrate all the data streams (e.g., chemistry, fate, exposures, hazards) into a final risk assessment and transparently document the decisions and assumptions made. This will facilitate the new chemicals program tracking decisions over time and evaluating consistency within and across chemistries.

External Peer Review & Outreach

Successful development and implementation of the five research areas will require outreach and peer review. As part of the outreach, EPA will engage in a dialogue with stakeholders to encourage collaboration, understanding and increased efficiencies in evaluating new chemicals under TSCA. The dialog will include seeking advice, comment, and help from stakeholders to accomplish the overall task of modernizing the process and bringing innovative science to evaluate new chemicals under TSCA. There will be several opportunities for peer review and public comment on the research plan as well as on individual deliverables from the research plan. The anticipated timeline and steps involved in the outreach and peer review of the research plan are as follows:

1. Seek input at an initial public meeting on April 20-21, 2022, to discuss this proposal. A Federal Register (FR) notice announcing the meeting was published on February 25, 2022 ([link](#)).
 - a. The meeting will be virtual and take place over two days (from 1 pm to approximately 5 pm EDT each day).
 - b. A webpage has been established to register for the meeting, with specific information on logistics, registering for oral public comment, and providing written comments ([link](#)).
2. Solicit peer review on a more detailed proposed plan from the Board of Scientific Counselors (BOSC) at a meeting to be held in the Fall 2022. The public will be able to provide oral comments at the BOSC on the detailed plan. Written comments on the detailed plan will be solicited.
3. Solicit additional peer review and public comment at multiple points in the development and implementation phases of the research. Although the peer review schedule may be adjusted as necessary in the future, at this time, OPPT anticipates the following:
 - a. Status update, discussion of challenges, possible revisions to initial plan (Year 3).
 - b. Completion of initial data collection and analyses and preliminary versions of new models and approaches (Year 5-6).
4. Publish the data and approaches from the research efforts in the open scientific literature (on-going).
5. Implement outreach through appropriate mechanisms (on-going): scientific societies, State and Tribal communications, internationally through the OECD and other mechanisms; and, public meetings to receive input and enhance transparency.