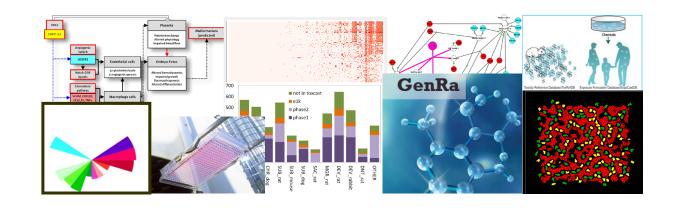
Navigating the Minefield of Computational Toxicology – Charting Progress from BluePrint to Implementation



5 June 2023

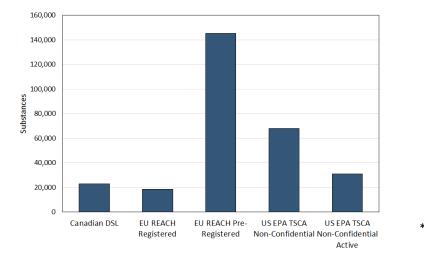
Grace Patlewicz Center for Computational Toxicology and Exposure Office of Research and Development

The views expressed in this presentation are those of the presenter and do not necessarily reflect the views or policies of the U.S. EPA



Why New Approach Methodologies (NAMs)?

Number of Substances

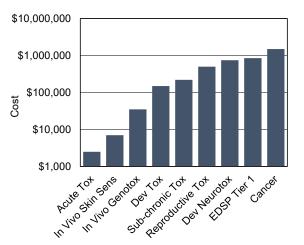


Amount of Data

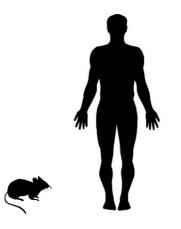
% of Non-Confidential, Active TSCA Inventory with Repeat Dose Toxicity Studies Yes 26%

*Data from ToxValDB

Economics



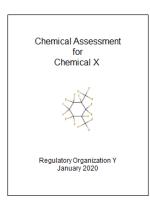
Reliability/Relevance



Broad Range of Decision Contexts Prioritization

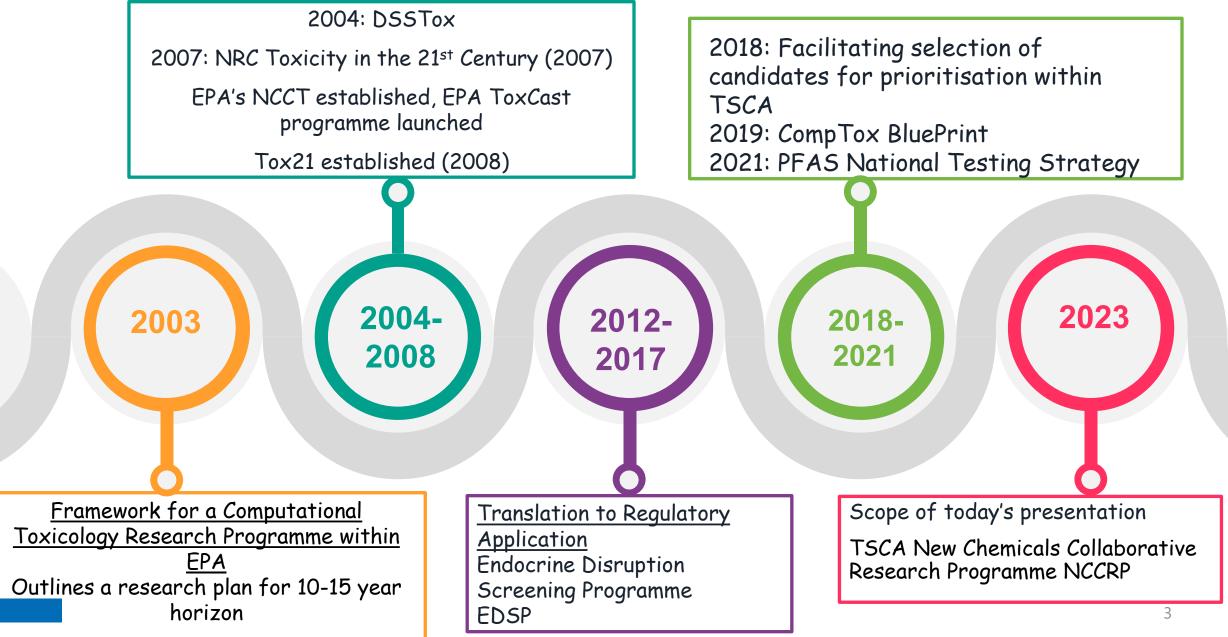


Time





Selected Milestones





EPA's CompTox Research BluePrint



TOXICOLOGICAL SCIENCES, 169(2), 2019, 317-332 doi: 10.1093/http://doi.org Advance Access Publication Date: March 5, 2019 Forum

FORUM

The Next Generation Blueprint of Computational

Toxicology at the U.S. Environmental Protection Agency

Russell S. Thomas,*,1 Tina Bahadori,† Timothy J. Buckley,‡ John Cowden,* Chad Deisenroth,* Kathie L. Dionisio,‡ Jeffrey B. Frithsen,§ Christopher M. Grulke,* Maureen R. Gwinn,* Joshua A. Harrill,* Mark Higuchi,¹ Keith A. Houck,* Michael F. Hughes,[¶] E. Sidney Hunter, III,[¶] Kristin K. Isaacs,[‡] Richard S. Judson,* Thomas B. Knudsen,* Jason C. Lambert, Monica Linnenbrink,* Todd M. Martin, || Seth R. Newton,[‡] Stephanie Padilla,[¶] Grace Patlewicz,^{*} Katie Paul-Friedman,* Katherine A. Phillips,[‡] Ann M. Richard,* Reeder Sams,* Timothy J. Shafer,¹ R. Woodrow Setzer,* Imran Shah,* Jane E. Simmons,¹ Steven O. Simmons,* Amar Singh,* Jon R. Sobus,* Mark Strynar,* Adam Swank,[‡] Rogelio Tornero-Valez,[‡] Elin M. Ulrich,[‡] Daniel L. Villeneuve,^{|||} John F. Wambaugh,* Barbara A. Wetmore,[‡] and Antony J. Williams*

National Center for Computational Toxicology, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, 'National Center for Environmental Assessment, U.S. Environmental Protection Agnecy, Washington, D.C. 20004, National Exposure Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, ⁸Chemical Safety for Sustainability National Research Program, U.S. Environmental Protection Agency, Washington, D.C. 20004, National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, National Center for Environmental Assessment, U.S. Environmental Protection Agency, Cincinnati, OH 45220, National Risk Management Research Laboratory, U.S. Environmental Protection Agency, Cincinn ati, OH 45220, and National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Duluth, MN 55804

¹To whom correspondence should be addressed at National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, 209 T.W. Alexander Drive, Room Di10-D, Mail Code, D143-02, Research Triangle Park, NC 27711. Park (919) 541-1194. E-mail: thomas russel lateps gov

Disclaimer: The U.S. Environmental Protection Agency has provided administrative review and has approved this article for publication. The views expressed in this article are those of the authors and do not necessarily reflect the views of the U.S. Environmental Protection Agency

ABSTRACT

The U.S. Environmental Protection Agency (EPA) is faced with the challenge of efficiently and credibly evaluating chemical safety often with limited or no available toxicity data. The expanding number of chemicals found in commerce and the environment, coupled with time and resource requirements for traditional toxicity testing and exposure characterization,

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317

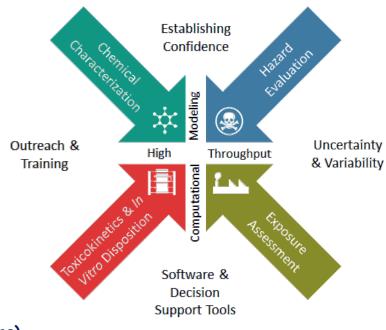
- DSSTox **Chemical library**
- Read across
- SAR/QSAR modeling
- Chemotypes
- TTC

•

- Literature Curation (ChemProp)
- Communities of Practice
- NAM Training courses/ videos

- HTTK assays (metabolism, bioavailability, binding)
- Partition coefficients
- HTTK R package
- Multi-route models
- Literature Curation (CvT)
- In vitro disposition

- Case Studies
- **Reference Materials**
- **Reporting Templates**



- CompTox Chemicals Dashboard
- RapidTox
- Factotum
- ECOTOX
- SegAPASS
- GenRA
- TEST

- In Vitro Assays (HTTr, HTPP, ToxCast)
- **Tiered** testing
- Organotypic models
- Addressing limitations (metabolism, chemical space)
- Statistical and Biologicallybased Modeling
- AOPs
- Literature Curation (ToxVal, ToxRefDB)
 - SEEM
 - ToxBoot
 - HTTK
 - ENTACT

- ExpoCast
- NTA/SSA
- Literature and External Source Curation (CPDat, CPCat, ChemExpoDB)
- Product emissivity



For Toxicology, NAM Development and Application are Being Integrated in a Tiered Framework

Broad Coverage,

High Content Assay(s)

Defined Biological Target

or Pathway

Select In Vitro

Assavs



TOXICOLOGICAL SCIENCES, 169(2), 2019, 317–332 doi: 10.1093/hoxsed/http58 Advance Access Publication Date: March 5, 2019 Fotum

FORUM

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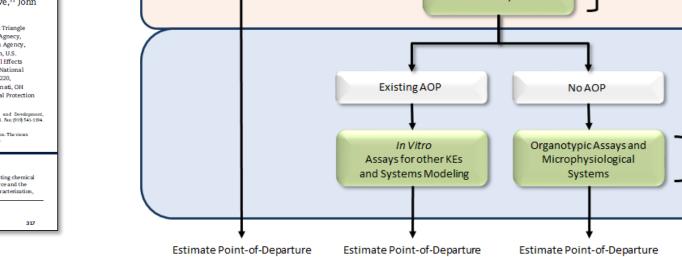
¹To whom correspondence should be addressed at National Gentur for Computational Toxicology, Office of Research and Development, U.S. EnvironmentalProtection Agency, 207 TW. Alexander Drive, Room Drill-D., Mail Gode: D545-02, Research Triangle Park, NC 2771. Rec (918) 543-1544. E-mail: homan-runal@Bopa.gov

Disclaimer: The U.S. Environmental Protection Agency has provided administrative review and has approved this article for publication. The views expressed in this article are those of the authors and do not necessarily mfact the views of the U.S. Environmental Protection Agency.

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Based on AOP

Based on Biological Pathway or Cellular Phenotype Perturbation

Chemical Structure

and Properties

No Defined Biological

Target or Pathway

Estimate Point-of-Departure Based on Likely Tissue- or Organ-level Effect without AOP

Multiple cell types

+/- metabolic competence

Orthogonal confirmation

Tier 1

Tier 2

Tier 3

Identify Likely Tissue,

Organ, or Organism Effect

and Susceptible Populations



Case Studies to Build Confidence and Help Translate to Regulatory Application

	TOXICOLOGICAL SCIENCES, 2019, 1-24	
OXFORD SOCT Society of Toxicology academic.oup.com/toxsci	dol: 10.1093/boxski/dr2001 Advance Access Fublication Date: September 18, 2019 Research Article	
Utility of In Vitro Bioactivity of In Vivo Adverse Effect Lev		
Prioritization	eis and in Risk-Based	
Katie Paul Friedman 🌑 ,* ¹¹ Matthew Ga Karamertzanis, ⁵ Tatiana Netzeva, ⁵ Tor M. Richard, [*] Ryan R. Lougee,* ^{II} Andrea Angrish, ^{III} Jean Lou Dorne, ^{IIII} Stiven Fo	nasz Sobanski, [§] Jill A. Franzosa, [¶] Ann	
Bahadori, [∥] Maureen R. Gwinn,* Jason Rasenberg. [§] Tara Barton-Maclaren,† a	OECD	
*National Center for Computational Toxicology, Office Protection Agency, Research Triangle Park, NC, 27711;	Organisation for Economic Co-operation and Development	ENV/JM/MONO(2019)28
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Disclaims: The bind States is instrumental interction Agency (U.S. 194). Agency administrativeries wan appendent for spatiations. Meeting of a Tak view expressed in this article are shown of the sushum and do not nee Canada, or the RC. ABSTRACT	CASE STUDY ON THE USE OF AN INT AND ASSESSMENT FOR ESTROGEN F	
Use of high-throughput, is with bioarthrity data in setting a pa- pace of human health safety evaluation by informing screeni to compare FOOD based on high-throughput predictions of bi information for 48 chemicals. FODs derived from new appro- using the 50th (FOD _{MMM} , so) and the 59th (FOD _{MMM} , so) percent Pablished by Cafoid University reas on behalf of the Society of Toxicology	Series on Testing and Assessment No. 300	
Places is by subsection of the section of the secti	The corresponding annexes are an ENV/JM/MONO(2019)28/ANN1	vailable under the following cotes:
	JT03450456	

Completed case studies

Center for Computational Toxicology & Exposure Ongoing and New Case Studies

- Use NAMs on selected pesticides with established MOAs
- Develop and apply NAMs for evaluating developmental neurotoxicity
- Integrating NAMs to screen candidates for prioritization under TSCA
- Application of *in vitro* bioactivity and HTTK for screening-level assessments in biosolids
- Prospective case study on application of *in vitro* assays for hazard characterization
- Using NAMs to inform chemical categorisation
- Computational approaches for rapid exposure estimates
- Using *in vitro* bioactivity to inform quantitative ecological hazard assessments
- Evaluating predictivity of HTTK methods



Toxicology & Exposure

under the Toxic Substanc Control Act (TSCA) Home

Basic Information

EPA's Review Process

Filing a Premanufacture Notice with EPA

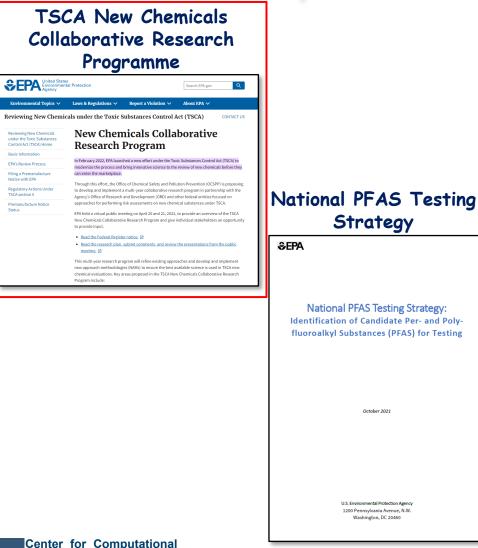
FSCA section 5

legulatory Actions Under

remanufacture Notice

Supporting the Regulatory Partners within EPA Using Computational Toxicology and Exposure in **Many Different Areas**

Using New Approaches to

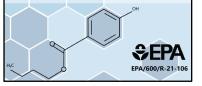


Evaluate Developmental Neurotoxicity for FQPA Environmental Topics 🗸 🛛 Laws & Regulations 🗸 Report a Violation 🗸 About EPA 🗸 elated Topics: FIFRA Scientific Advisory Pane The use of new approach methodologies (NAMs) to derive extrapolation factors and evaluate developmental neurotoxicity for human health risk assessment Full Peer Review Meeting: EPA held a public meeting of the FIFRA Scientific Advisory Panel on Sept 15-17, 2020 to consider and review e use of new approach methodologies (NAMS) to derive extrapolation factors and evaluate developmental neurotoxicity for huma wealth risk assessment (read the Federal Register notice [2]). reparatory Virtual Meeting: EPA held a preparatory virtual meeting for the SAP members and the public to o regarding the scope and clarity of the draft charge questions to be used for the peer review on August 25, 2020. View the igenda ☑ and the presentation ☑ for the August 25 meeting. Meeting Materials Click here 🕜 for the agenda Click here 12 for the charge questions lick here 🗹 for the Meeting Minutes and Final Repor ther materials, including EPA's background paper, are available for public comment in the EPA docket 🗹 for this meeting, except fo he following ZIP files which are available below: The B nam, public, code, may2020 zin (zin) file (32 MB) I contains the statistical analyses of development neurotoxicity new approach methodologies (NAMs) described in Section 2.3.4-2.3.6 of the Agency's Issue Paper and a ReadMe file with zip folder details. The CEBanalysesSept2020 sap.zip (zip) o file (10 MB) includes the statistical analyses of in vitro inhibition kinetics data des in Section 3.2.2 and Section 3.3 of the Agency's Issue Paper and a ReadMe file with zip folder details Laws & Regulations 🗸 Report a Violation 🗸 Endocrine Disruption **Endocrine Disruptor Screening** Endocrine Disruption Home Learn About Endocrine Program (EDSP) Policies and Procedures Program Overview On this page: Regulatory Resource Use of High Throughput Assays and Computational Tools Policies and Procedures for Screening Pesticides Chemical Screening an Festing Progress · Policies and Procedures for Screening Safe Drinking Water Act Chemicals Work Plan to Improve Evaluation of Chemicals in the Endocrine Disruptor Use of High Throughput Assays and Computational Tools Based on scientific advances, EPA intends to implement the use of high throughput assays and computational models to evaluate, and to a significant extent, screen chemicals. These sensitive, specific, quantitative, and efficient screening methods will rapidly screen many hemicals and substantially decrease costs and animal use and may be used as an alternative to some EDSP Tier 1 screening assays, ToxCast[®] To improve efficiencies in screening and testing chemicals, EPA scientists are helping to evolutionize chemical screening and safety testing based on advar toxicology. A major part of this effort is the Agency's Toxicity Forecaster, or ToxCast™, which uses automated, robotics-assisted high throughput assays to expose living cells or proteins to hemicals and measure the results. The high throughput assays produce cor response information representing the relationship between chemical concentration an

Prioritising Existing Chemicals Under **TSCA**



A Proof-of-Concept Study Integrating Publicly Available Information to Screen **Candidates for Chemical** Prioritization under TSCA



Endocrine Disruptor Screening Programme



Background on TSCA and New Chemical Evaluations

- The TSCA New Chemicals program serves a "gatekeeper" role to manage potential risk to human health and environment from chemicals new to the marketplace; EPA receives ~ 500 new chemical submissions annually.
- TSCA section 5 requires that any person planning to manufacture or import a non-exempt new chemical substance (i.e., a chemical not on the TSCA Inventory) notify EPA before beginning that activity. This notice is known as a premanufacture notice (PMN).



Background on TSCA and New Chemical Evaluations

- EPA is generally required to review these PMNs within 90 days, which consists of assessing the potential risks to human health and the environment of the chemical under the conditions of use, and to make an affirmative determination.
- Where the chemical substance presents or may present an unreasonable risk, EPA must take action to prevent those risks before the chemical can enter commerce.



Challenges and Opportunities in New Chemical Evaluations

- New chemical submissions typically lack chemical-specific data on human and environmental hazards, exposure, physical chemical properties and environmental fate/transport.
- EPA must make an affirmative determination for all new chemical submissions within the 90-day time period.
- EPA must evaluate new chemical risks under intended, known, and reasonably foreseen conditions of use.



Challenges and Opportunities in New Chemical Evaluations

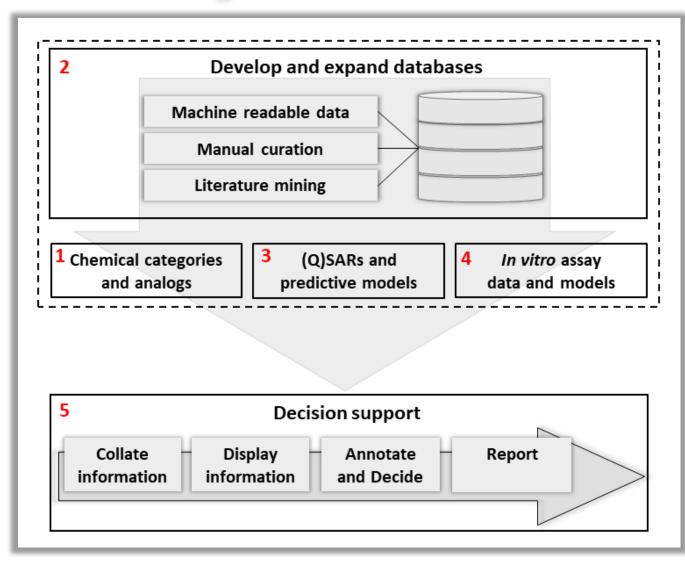
- EPA's chemical data management infrastructure is outdated. Chemical safety data submissions are scattered across multiple databases, file management systems, and paper files making searches and integration of chemical information inefficient and time consuming.
- EPA is required to reduce and replace vertebrate animal testing.

New approach methods (NAMs), along with data curation and decision support tools, may address additional hazard data gaps, identify potential conditions of use, and furnish more information for making the required determination



Focus Areas in the TSCA New Chemicals Collaborative Research Programme

- 1) Update and refine chemical categories
- 2) Develop and expand databases containing TSCA chemical information
- 3) Develop and refine (Q)SAR and predictive models for physicochemical properties, environmental fate/transport, hazard, exposure, and toxicokinetics
- 4) Explore ways to integrate and apply NAMs in New Chemical Assessments
- 5) Develop a TSCA new chemicals decision support tool to modernize the process



https://epa.figshare.com/articles/code/PubMed_Abstract_Sifter/10324379

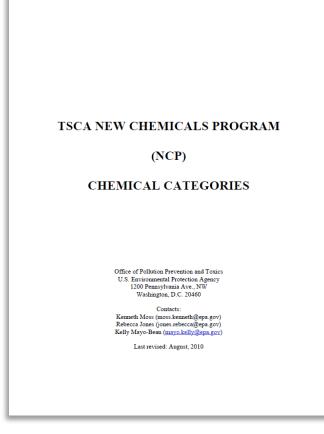


Update and refine chemical categories

	Research Area	Challenge	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; physicochemical 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.



Update and refine chemical categories

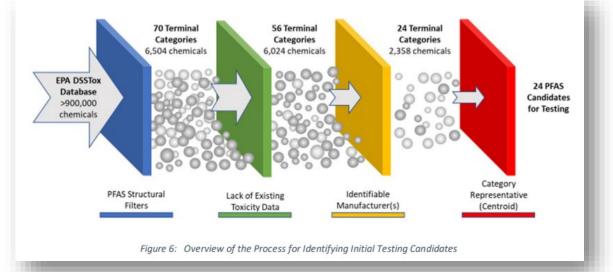


- 56 existing NCCs are characterised largely by structural features and in some cases by physicochemical properties.
- The chemical categories are used to identify potential hazard concerns and testing strategies for new chemical submissions.
- The key goals of collaborative research in this area are to implement the chemical categories in a transparent and reproducible manner that would permit updates with new information, such as additional structure descriptors, physicochemical data, or NAM data.
- Further, planned research will investigate to what extent new categories are needed to capture substances in the TSCA active inventory that could not be readily assigned to one of the 56 existing NCCs.

https://www.epa.gov/reviewing-new-chemicals-under-toxicsubstances-control-act-tsca/chemical-categories-used-review-new

Update and refine chemical categories

National PFAS Testing Strategy: Identification of Candidate Per- and Poly-fluoroalkyl Substances (PFAS) for Testing (October 2021)

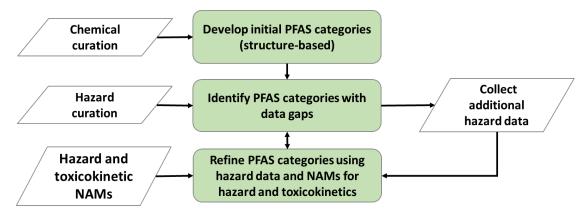


<u>https://www.epa.gov/system/files/documents/2021-10/pfas-natl-test-</u> <u>strategy.pdf</u>

Category research will help address additional questions:

- To what extent the TSCA chemicals fall within the applicability domain for existing (Q)SAR models or structural alert scheme.
- What is a proof-of-principle scheme using chemical categories, read-across, and (Q)SARs to inform in silico evaluation of the TSCA active inventory?

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Chemical categories may be developed by a combination of one or more of the following:

- structural descriptors,
- physicochemical properties,
- predicted metabolism,
- in vitro mechanistic and toxicokinetic, and/or
- *in vivo* toxicity data (human or ecological health).



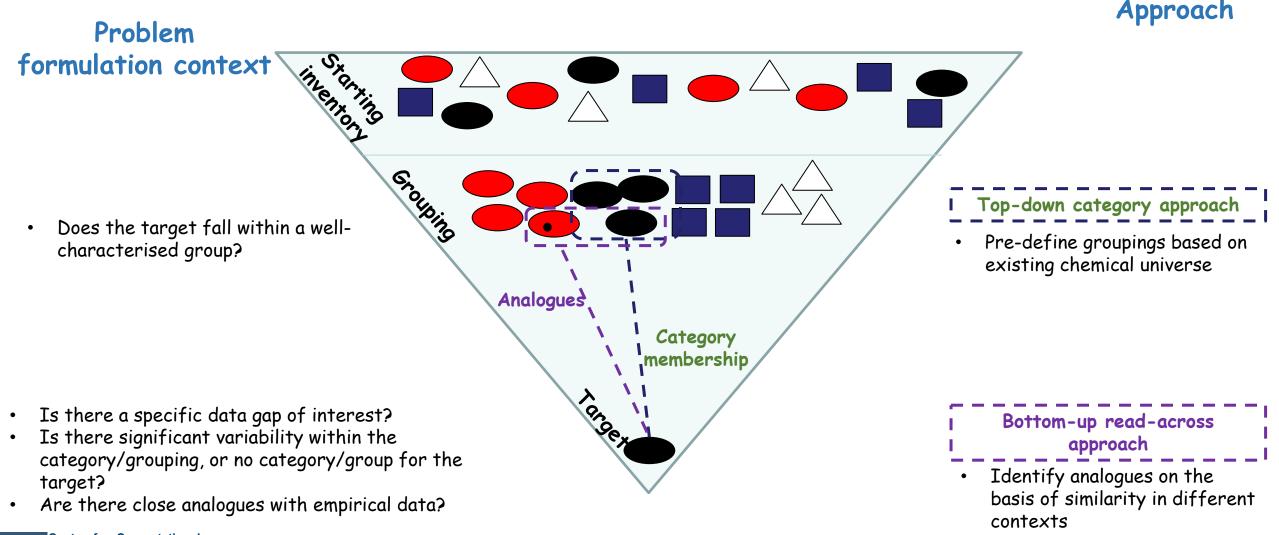
Existing new chemical categories (NCCs) will be turned into a machine- readable format, facilitating profiling Environmental Protection and comparison initial

- Structure information bui into the current NCCs will turned into a machinereadable format to enable substructure searching an mapping to other types of structural descriptors, su as ToxPrints (Yang et al., 2015).
- The TSCA non-confidentia active chemical inventory be profiled using the newly codified NCCs to assign th into their respective categories.
- Here, we show an example translating AIM fragments to machine read-able format.

Fragment	Number	fragme Modified Name	General Comments	Structure		
	Number	Woulled Name				
-CH3 [aliphatic carbon]	0	Methyl; Primary carbon		R ^{CH3}		
-CH2- [aliphatic carbon]	1	Secondary carbon		R I R ^{CH} 2	Chemical Subgraphs and Reactions A Language (CSRML) [used for ToxP	
-CH (aliphatic carbon)	2	Tertiary carbon		R I R ^{CH} R	0 1 1 2 2	_
C [aliphatic carbon - No H, not tert]	3	Quaternary carbon		R H C R R	с с с	
=CH2 [olefinic carbon]	4	Alkene		R ^{≠CH₂}	3 4 3_a 5 3_b	
=CH- or =C< [olefinc carbon]	5	Vinyl	R's are undefined		C=N C ² ? C=N C ²	C
#C [acetylenic carbon]	6	Alkyne		R ^{EC-R'}	4 7 5 8 6	

This research will enable computational approaches to chemical grouping based on one or more types of structural descriptor(s) as well as other pertinent information.

Categories and read-across are two complementary Strategies for approaching data-gap filling for data poor chemicals

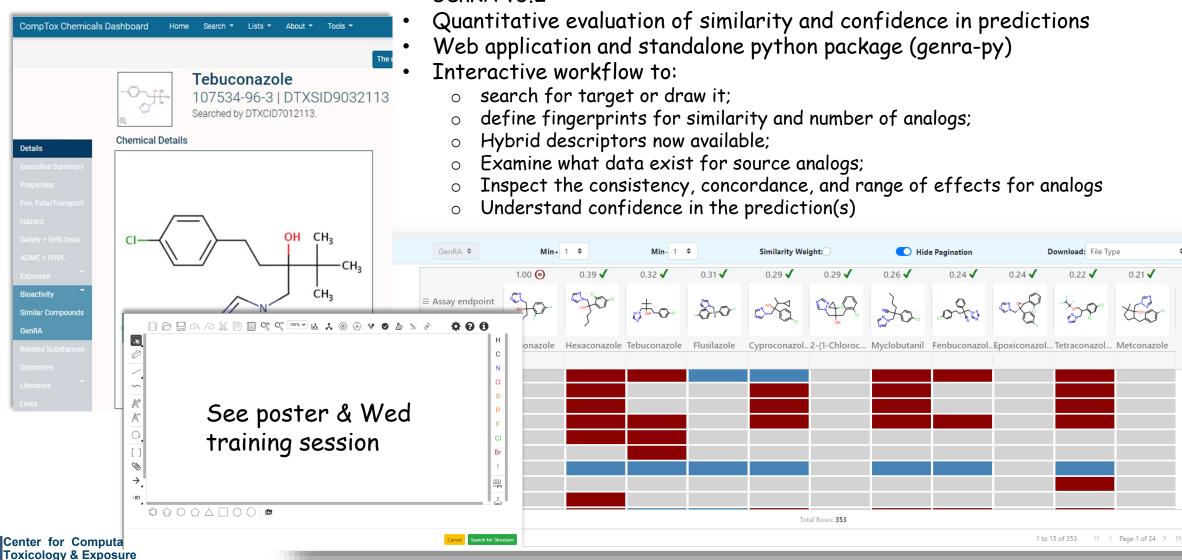




Currently available public tools for systematic read-across may be informative

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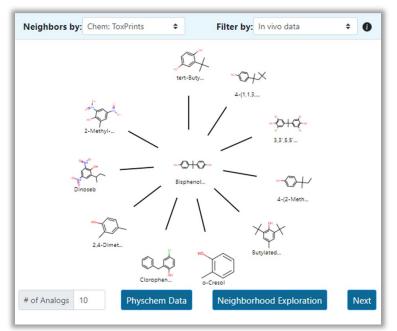
• GenRA v3.2



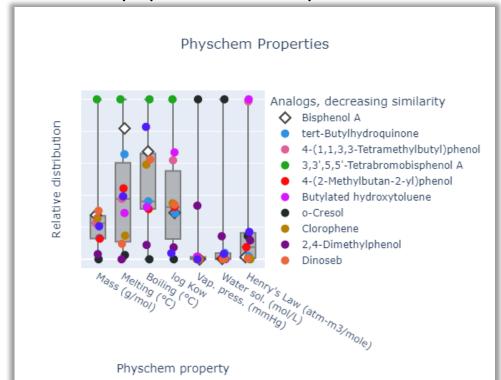


GenRA capabilities will continue to be expanded in Research Area 1

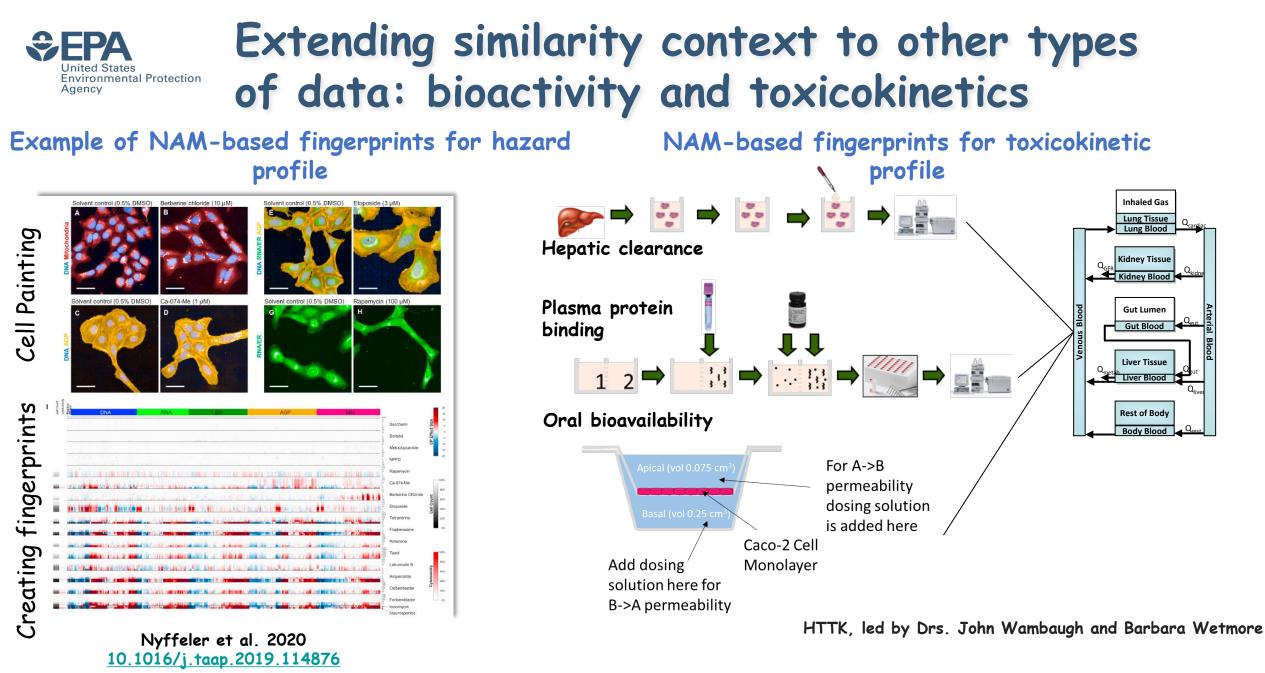
Different fingerprint types and fingerprint hybrids can be used to define neighbourhoods of chemicals associated with available hazard data



Research will examine the impact of hybrid features on GenRA performance Some analogues defined by one or more fingerprint methods may have more similar physicochemical profiles



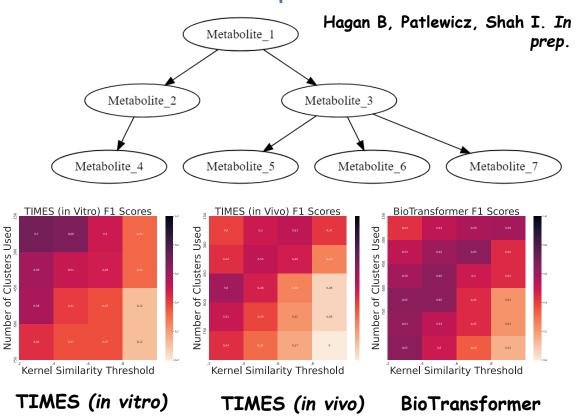
Research will extend similarity contexts to additional types of bioactivity, toxicokinetic, and metabolism data to inform analogue identification and evaluation



EPA United States Environmental Protection Agency Extending similarity context to other types of data: metabolism and metabolites

How to leverage information about the metabolic pathways of substances in order to increase confidence in toxicological assessment via read-across

- Metabolic similarity is an important consideration in evaluating analogue suitability in read-across, but current practice often relies on expert judgement and/or empirical (*in vivo*) metabolism data.
- As empirical metabolism data is limited, we will make use of predicted metabolism data from different tools such as BioTransformer and TIMES. How well these tools perform relative to reported empirical data will be evaluated.
- One approach being explored to codify 'metabolic information' is to construct metabolic graphs from the predictions generated from different tools and evaluate their similarity with different metrics such as kernel approaches.



Comparing the correspondence between structural analogues pairs vs using kernel approach

Metabolic Graph Construction



Summary of Research Area 1

- Produce a computational approach to chemical grouping into categories based on structure and other descriptors, including structural descriptors, physicochemical and environmental fate properties, predicted metabolism and/or metabolites, NAM-based hazard and toxicokinetic information, and/or in vivo hazard data (human and/or ecological health)
- Continue enhancing GenRA capabilities to include:
 - evaluating the impact of hybrid features on GenRA performance;
 - extending similarity contexts to additional types of bioactivity data;
 - evaluating the contribution of metabolism data to inform analogue identification and evaluation; and,
 - additional case studies to build confidence in the use of GenRA versus other readacross approaches
- Characterise the chemical structure space encompassed within the TSCA nonconfidential active chemical inventory and evaluate to what extent the chemicals on this inventory fall within the applicability domain for (Q)SAR models or other structural alert schemes (either existing or in development)

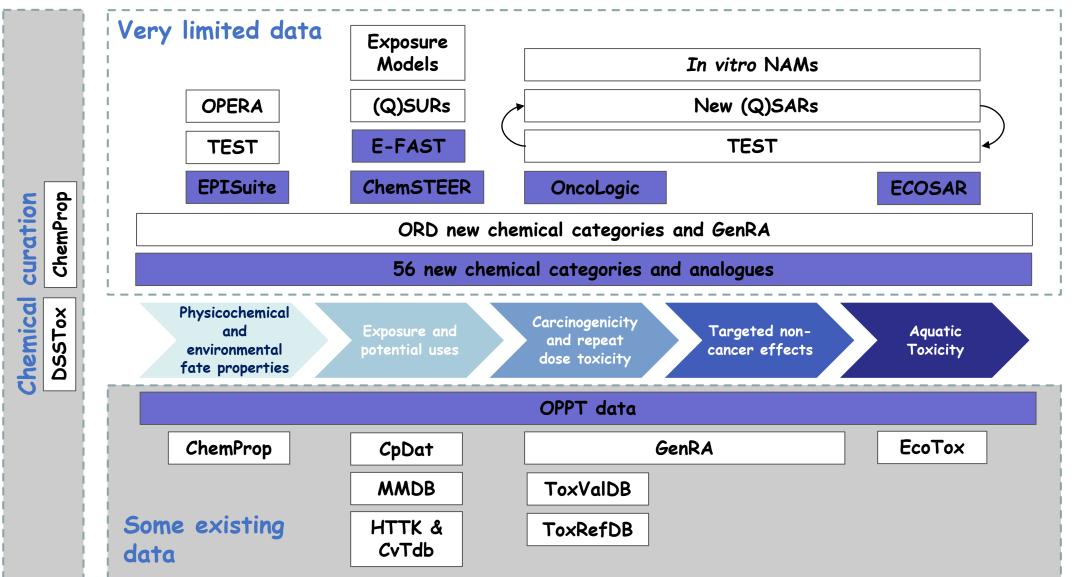


Research Area 2

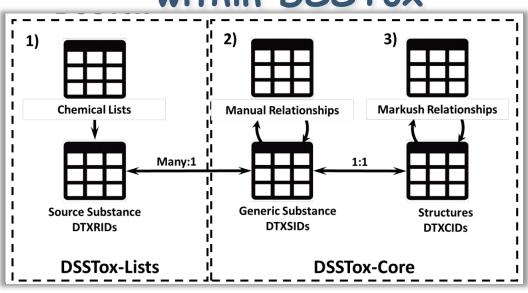
Resear	rch Area	Challenge	Approach	Expected Outcome(s)
Chemi	d ases ining TSCA	Existing TSCA information is not computationally accessible or easily searchable	Continue extraction and curation of physical-chemical property, environmental fate, hazard, and exposure information (non-CBI) in ORD databases Map information in ORD databases to standardised reporting templates and store in an International Uniform Chemical Information Database (IUCLID)	Publicly available sources can expand the amount of information available, enhancing chemical reviews and enabling efficient sharing of chemical information across EPA.



Different data scenarios









- >1.2 million unique substances
- Informs accurate structure-data linkages for screening projects, read-across, non-targeted analysis, structurebased modeling

As the TSCA active inventory of chemicals grows each year, expansion of the DSSTox database to include these chemicals as well as existing and emerging chemicals of interest for modeling applications is essential.

- Curation enables programmatic access to any data that can be linked to a DSSTox identifier.
- New chemical submissions under TSCA may be for defined or complex mixtures, and chemistry curation can provide solutions for better linking appropriate data to these mixtures to facilitate read-across or other downstream predictions (e.g., PFAS, substances of unknown or variable composition, complex reaction products and biological materials).

As more chemicals are added to the TSCA active nonconfidential inventory, or chemistries with limited available information are identified, more structure, physicochemical, and environmental fate property data curation is needed to support decision making and data interoperability.

Center for Computational Toxicology & Exposure

Agency

DSSTox = Distributed Structure-Searchable Toxicity (database)

Expanded physicochemical and environmental fate Prote properties and predictions inform (Q)SARs: ChemProp

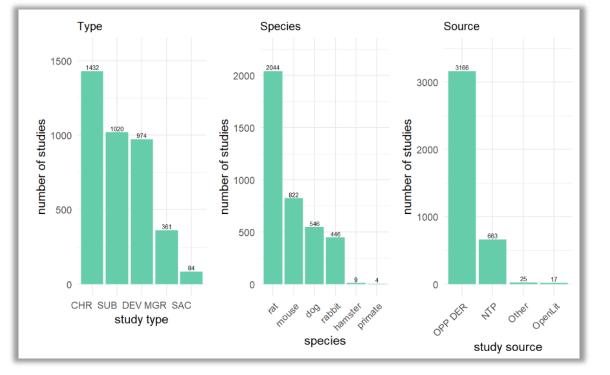
- ChemProp stores both experimental and predicted physicochemical and environmental fate property data for access by applications such as the CompTox Chemicals Dashboard and (Q)SAR development.
- Experimental data have been harvested and curated from online sources such as the PHYSPROP database, ECOTOX, online public sources (eChemportal, PubChem, LookChem, OChem), and peer-reviewed literature.
- Predicted data are generated using OPERA, TEST, EPISuite, ECOSAR, and ACD/Labs.

Making forward predictions of these properties for new chemical submissions may improve with more curated data from existing TSCA-relevant chemicals.

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Expanding databases with hazard data will improve in silico United States Agency Agency Expanding databases with hazard data will improve in silico approaches, including (Q)SAR and read-across, for new chemical evaluation: ToxRefDB Includes guideline or guideline-like studies with

ToxRefDB v2.1 contains summary information for 1143 chemicals and 5986 studies, with quantitative dose-response data extracted for 3871 studies.

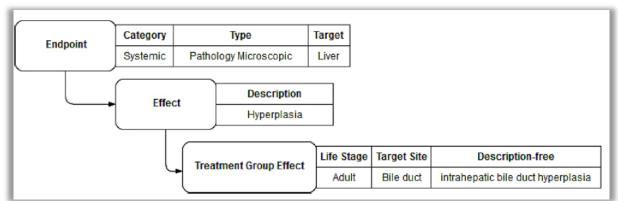


The study designs with highest frequency in the database include chronic (CHR), sub-chronic (SUB), developmental (DEV), subacute (SAC), multigeneration reproductive (MGR.

Credit Madison Feshuk, Dr. Katie Paul Friedman, Dr. Sean Watford

Center for Computational Toxicology & Exposure <u>https://doi.org/10.23645/epacomptox.6062545.v4</u> Includes guideline or guideline-like studies, with guideline profiles developed for OCSPP series 870 Health Effects and some NTP study types to allow inference of negative effects

- Study design and meta-data, dose-response data, and detailed effect terminology linked to study type/guideline
- Standardised effect terminology developed for ToxRefDB mapped to terms from the United Medical Language System (UMLS)
- An application was developed to manage two curator and manager reviews of manually curated data from source



ToxRefDB v2.0: Watford S et al. 2019 DOI <u>10.1016/j.reprotox.2019.07.012</u>

²⁷

Expanding databases with hazard data will improve in silico United States Environmental Protection approaches, including (Q)SAR and read-across, for new chemical evaluation: ToxVaIDB

- ToxValDB is a collection of quantitative information on chemicals and *in vivo* toxicology summary values
 - Experimental in vivo toxicology records
 - PODs (LOAEL, NOAEL, BMD), effects, species, exposure routes, study types
 - Human health and ecological health
 - Example sources: HPVIS, ToxRefDB, ECOTOX, HAWC, EFSA, ECHA, COSMOS, HESS
 - Risk assessments
 - RfD, RfC, cancer slope factors, caner unit risk
 - Example sources; IRIS, PPRTV, ATSDR, Cal OEHHA
 - Air, water and soil quality values, worker exposure limits
 - Example sources: RSL, OSHA, NIOSH
- Data is computationally extracted from source documents / databases and mapped to common terms
- Currently, 47 sources and > 50,000 chemicals with at least one value (ToxValDB v9.2).
- ToxValDB v9.4 about to be released

CompTox Chemica	ls Dashboard Hom	e Search - Lists				
		Searched by DTXS	XSID7020182			
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Bioactivity	B 3 ECHA eChe		developmental =	0.200 mg/kg-day	developmental	oral
Similar Compounds	B 3 ECHA eChe		reproduction =	0.200 mg/kg-day	reproduction	oral
GenRA	B 3 ECHA eChe		reproduction =	0.200 mg/kg-day 0.200 mg/kg-day	reproduction	oral
	B 3 ECHA eChe		short-term =	600 mg/kg-day	short-term	oral
Related Substances	B 3 ECHA eChe		repeat dose =	30.0 ppm	repeat dose	oral
Synonyms	B 3 ECHA eChe		repeat dose =	300 ppm 75.0 ppm	repeat dose	oral
Literature	B 3 ECHA eChe		repeat dose =	750 ppm	repeat dose	oral
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https://doi.org/10.23645/epacomptox.20394501.v3



Summary of Research Area 2

Chemical data for TSCA-relevant chemicals will be curated across the myriad ongoing curation activities in ORD

Data type curated	Relevant Database(s) and links to full data
Chemistry and properties	DSSTox, ChemProp: <u>https://comptox.epa.gov/dashboard/</u>
In vivo hazard in human health	ToxRefDB: <u>https://doi.org/10.23645/epacomptox.6062545.v4</u>
relevant models	ToxValDB: <u>https://doi.org/10.23645/epacomptox.20394501.v3</u>
In vivo hazard in ecologically	ECOTOX Knowledgebase: <u>www.epa.gov/ecotox</u>
relevant species	
Monitoring, release, and	MMDB: <u>https://clowder.edap-</u>
product information for	cluster.com/datasets/606cc2bd9932c7c0b50a73af
exposure	CpDat: <u>https://doi.org/10.23645/epacomptox.5352997</u>
Toxicokinetic data	HTTK: <u>https://cran.r-project.org/web/packages/httk/index.html</u> CvTdb: <u>https://github.com/USEPA/CompTox-PK-CvTdb</u>

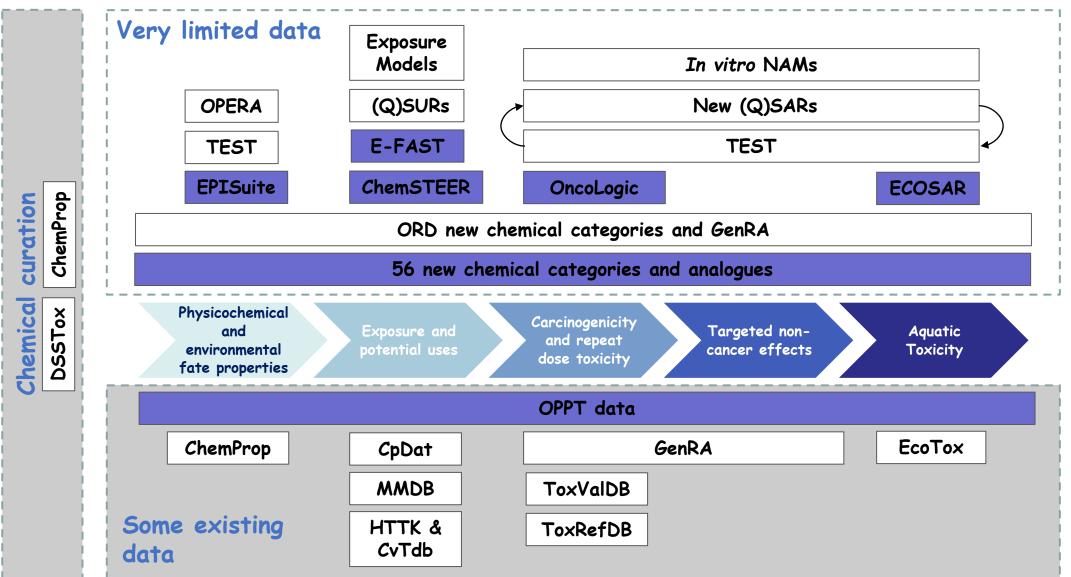


Research Area 3

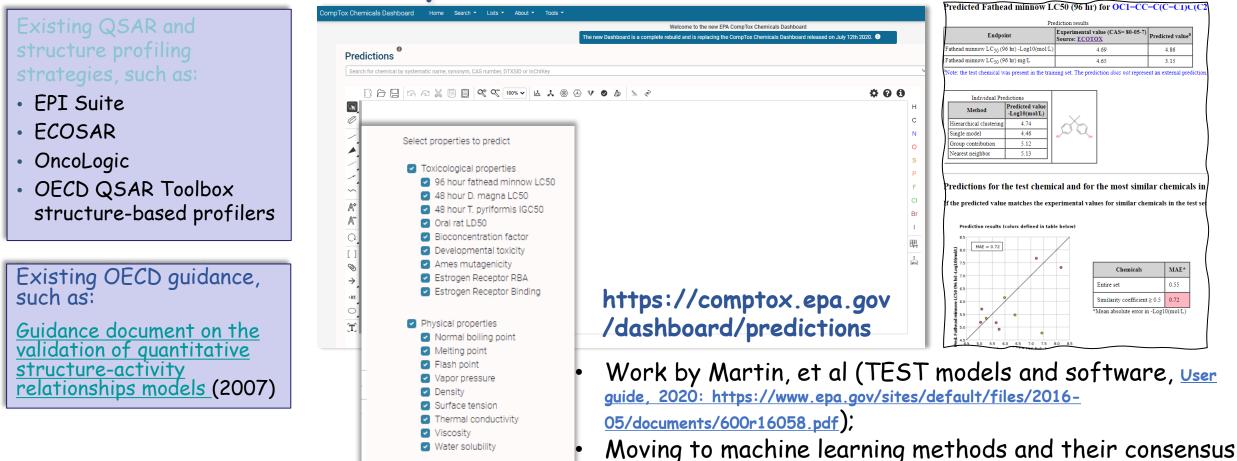
	Research Area	Challenge	Approach	Expected Outcome(s)
3	Develop and Refine QSAR and Predictive Models for Physical- Chemical Properties, Environmental Fate/Transport, Hazard, Exposure, and Toxicokinetics	Currently used models are not always publicly accessible, easy to update with additional chemicals, 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, increase transparency, and a process for updating these models as science allows.



Different data scenarios



Existing use of QSAR and structure alerts can be United States Environmental Protection enhanced by ongoing work in ORD to publish QSARs for real-time prediction



predictions

Make models and their performance reports publicly

available, including evaluation of applicability domain

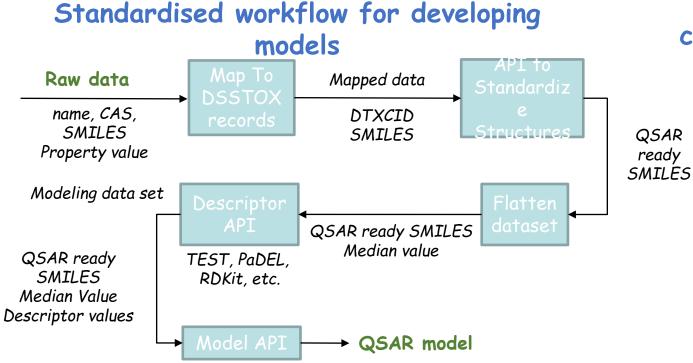
Water solubility

CALCULATE

See presentation by Drs Martin & Charest

32

WebTEST2.0 as a model registration and model nited States Environmental Protection development platform Agency



Capability to build machine-learning and consensus models within the WebTEST2.0 platform

- Python-based machine learning methods including:
 - RF Random Forest
 - SVM Support Vector Machine
 - DNN Deep Neural Network
 - XGBoost eXtreme Gradient Boosting
 - kNN- k nearest neighbors
- Consensus of machine-learning methods
 - Consensus average of above methods

- RF, SVM, DNN, etc. Each (Q)SAR model is associated with a versioned data set, (Q)SAR methodology, and molecular descriptor set (all stored in a database) so that the predictions are reproducible
- Easily implementable as web services for both model building and real-time model prediction that will provide deployable (Q)SAR models with appropriate documentation.



- Models for physicochemical properties (e.g., octanol water partition coefficient (logKow), vapor pressure, and Henry's law constant) are being developed using the WebTEST2.0 workflow.
- Revised toxicity models will be developed by expanding the toxicity datasets for WebTEST1.0 (*e.g.*, acute aquatic toxicity).
- In addition, models will be developed for additional toxicity endpoints (*e.g.*, carcinogenicity, repeat dose toxicity, skin sensitisation) to support TSCA new chemical evaluations.



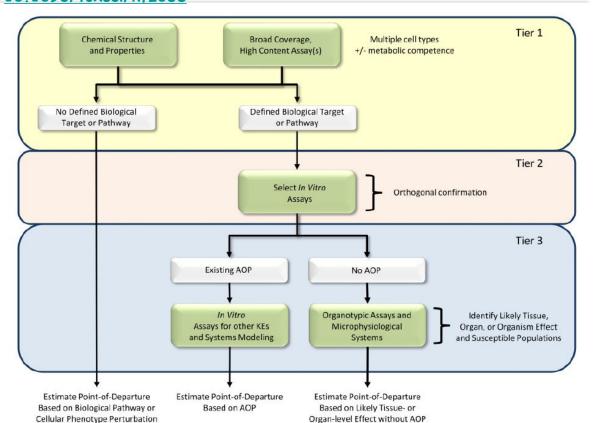
- Add externally developed models via web services
 - Models developed outside of the WebTEST platform will be implemented via Docker containers or via API calls to external webservices.
 - OPERA, EPI Suite, and WebTEST1.0 models will be incorporated into WebTEST2.0 via webservices.
 - Additionally, bioactivity-based models for estrogen receptor (Judson et al., 2017; Judson et al., 2015), androgen receptor (Judson et al., 2020; Kleinstreuer et al., 2017), steroidogenesis (Haggard et al., 2018; Haggard et al., 2019), and potentially other bioactivities based on *in vitro* NAM data, will be included in the WebTEST2.0 model registration platform.
 - Registration of all models, regardless of their development within or outside of the WebTEST platform, will include meta-data on the input features used in the modeling, the model output, and version information about that model; this constitutes an important goal for WebTEST2.0 and for rapid integration of information from disparate sources for next generation risk assessment.



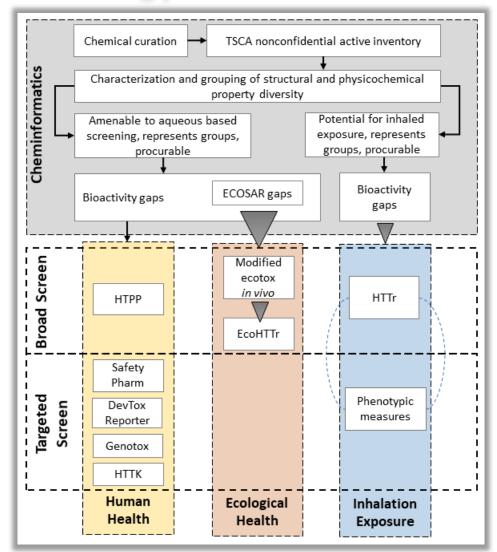
	Research Area	Challenge	Approach	Expected Outcome(s)
4	Explore Ways to Integrate and Apply NAMs in New Chemical Assessments	Reduction in the use of vertebrate animals in accordance with TSCA Section 4(h) Many PMN submissions are data poor Amended TSCA requires affirmative determination regarding unreasonable 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

Research Area 4 will combine broad and targeted screens United States Agency Agency Research Area 4 will combine broad and targeted screens to inform estimates of a bioactivity-based point-ofdeparture and address specific biology

Thomas et al. 2019 10.1093/toxsci/kfz058

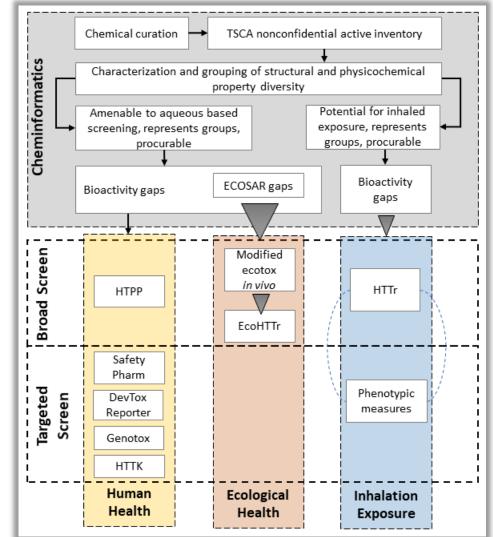


In Research Area 4, ORD will collect in vitro NAM data to demonstrate how NAMs for bioactivity and toxicokinetics can be used in a NAM-informed assessment of data-poor chemicals.



Cheminformatics and reference chemical knowledge will Duited States Environmental Protection Agency Cheminformatics and reference chemical knowledge will drive the selection of 200-300 chemicals for an initial case study

- In a first step, ORD will focus on development of a dataset for 200-300 chemicals, including some reference chemicals as well as TSCA-relevant chemicals from the nonconfidential inventory, to increase scientific confidence in application of this suite of bioactivity NAMs for informing chemical safety.
- These data will be needed to evaluate performance of these NAMs for further application and may also inform evolving frameworks for using multiple data streams to inform bioactivity-based dose-response assessment and hazard identification.



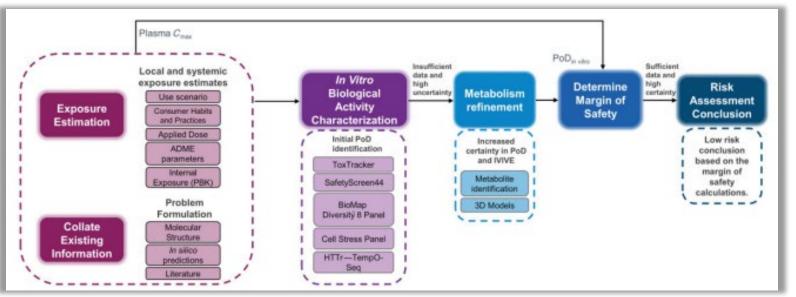


	R	Research Area	Challenge	Approach	Expected Outcome(s)
5	N D t N	New Chemicals Decision Suppor Tool to	Searching, collating, and integrating data for new chemical assessments is inefficient and costly	Build proof of concept software workflow that integrates all data streams in a new chemical risk decision 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.



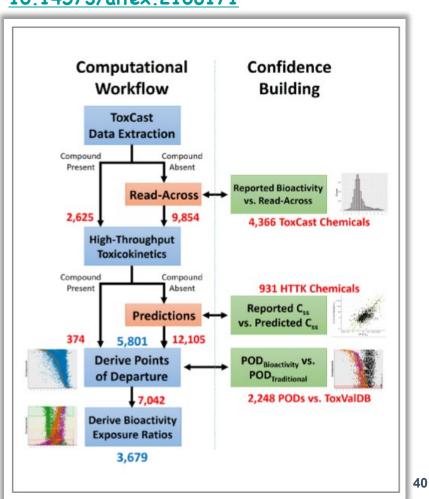
Examples of next generation risk assessment workflows that incorporate NAMs

Baltazar et al. 2020, "A Next Generation Risk Assessment Case Study for Coumarin in Cosmetic Products." <u>10.1093/toxsci/kfaa048</u>

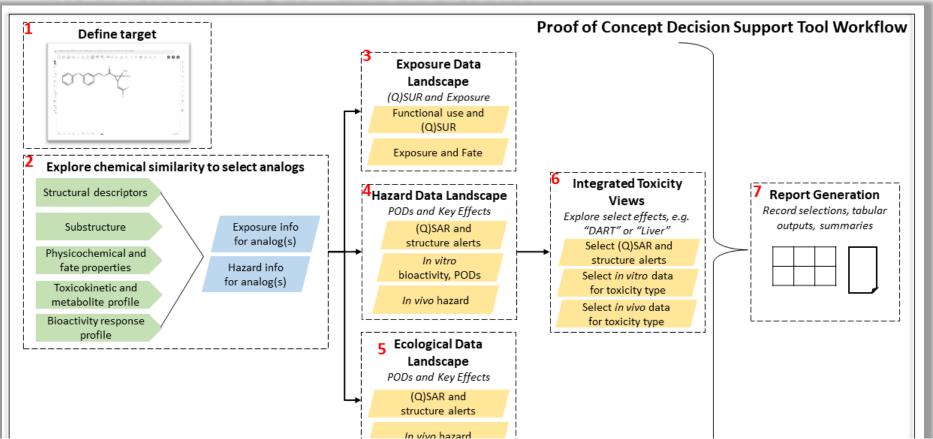


- Customised, modular decision support tool will be needed
- Blend existing data and models with NAMs
- Software that allows user to interact with data, make selections, and record these selections

Beal et al. 2020, "Implementing in vitro bioactivity data to modernize priority setting of chemical inventories." 10.14573/altex.2106171



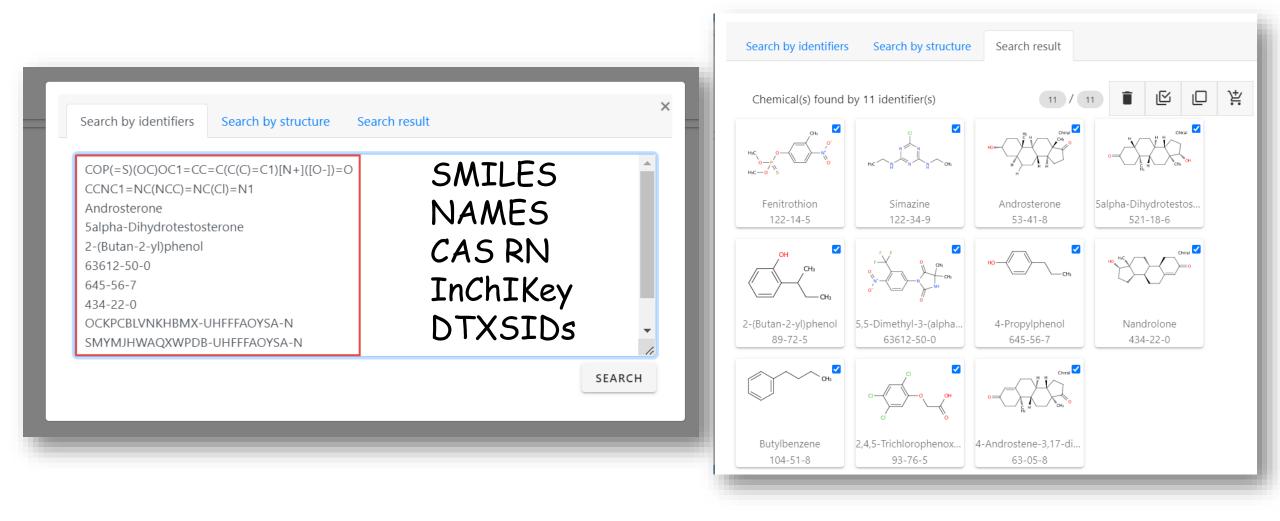
EPA United States Environmental Protection Agency Components of a proof-of-concept decision support tool may include modules to display, select, and download key information for assessment



Overall, this collaboration to support digitisation, integration, and ultimate conversion to IUCLIDcompatible formats will support collation of these data for utilisation by applications, such as a decision support tool.



Cheminformatics PoC Modules could be adapted to address NCCRP tools





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Easy export of all data to Excel or United States Environmental Protection Agency SDF

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Work of the NCCRP has begun in earnest

- Research during the 2023-2026 timeline will provide a foundation for continued improvement to meet the needs of new chemicals evaluation.
- Complement the EPA NAMs WorkPlan:
 - modernise available approaches, including decision support tools, for new chemicals evaluation
 - impact the engineering of the databases, models, and tools that ORD is building for multiple stakeholders to execute the vision of the CompTox BluePrint (Thomas et al., 2019) and the EPA NAMs WorkPlan (USEPA, 2021b)
- Achieve common goals:
 - -greater acceptance and scientific confidence in NAMs applied within the NCCRP;
 - -greater understanding of the future needs of NAM development; and
 - decision support tools that provide consistent, but iteratively improving, access to and integration of myriad data sources with chemical information, including data derived from NAMs
- Build external partnerships:
 - OPPT, ORD, and NIH (DTT/NIEHS, NICEATM, and NCATS)
 - Other regulatory partners, such as ECHA



EPA Core Planning Team

OCSPP Madison Le Shari Barash Jeff Dawson Anna Lowit Louis Scarano Tala Henry Keith Salazar Meghan Tierney Stan Barone Kellie Fay Martin Phillips Keith Avery

ORD

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Katie Paul Friedman **Kristin Isaacs** Caroline Ring Katherine Phillips John Wambaugh Antony Williams **Grace** Patlewicz Todd Martin Nate Charest Dale Hoff **Brett Blackwell Richard Kolanczyk Risa Sayre** Norm Adkins Madison Feshuk

Shaun McCullough Mark Higuchi Dan Villeneuve Kevin Flynn Chad Deisenroth Joshua Harrill **Richard Judson** Sean Watford Jill Franzosa **Tim Buckley** Sid Hunter Peter Egeghy Michael DeVito Jonathan Wall

And more...