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Review article

Cutting-edge computational chemical exposure research at the U.S. Environmental Protection Agency

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ABSTRACT

Exposure science is evolving from its traditional "after the fact" and "one chemical at a time" approach to forecasting chemical exposures rapidly enough to keep pace with the constantly expanding landscape of chemicals and exposures. In this article, we provide an overview of the approaches, accomplishments, and plans for advancing computational exposure science within the U.S. Environmental Protection Agency's Office of Research and Development (EPA/ORD). First, to characterize the universe of chemicals in commerce and the environment, a carefully curated, web-accessible chemical resource has been created. This DSSTox database unambiguously identifies >1.2 million unique substances reflecting potential environmental and human exposures and includes computationally accessible links to each compound's corresponding data resources. Next, EPA is developing, applying, and evaluating predictive exposure models. These models increasingly rely on data, computational tools like quantitative structure activity relationship (QSAR) models, and machine learning/artificial intelligence to provide timely and efficient prediction of chemical exposure (and associated uncertainty) for thousands of chemicals at a time. Integral to this modeling effort, EPA is developing data resources across the exposure continuum that includes application of high-resolution mass spectrometry (HRMS) non-targeted analysis (NTA) methods providing measurement capability at scale with the number of chemicals in commerce. These research efforts are integrated and well-tailored to support population exposure assessment to prioritize chemicals for exposure as a critical input to risk management. In addition, the exposure forecasts will allow a wide variety of stakeholders to explore sustainable initiatives like green chemistry to achieve economic, social, and environmental prosperity and protection of future generations.

1. Background/introduction

Computational exposure science represents a line of research that is both quickly advancing and critically needed for protecting human health and the environment (Cohen Hubal et al., 2010; Egeghy et al., 2016). Traditional single-chemical, retrospective exposure assessment approaches are no longer adequate to manage the enormous number of existing and new chemicals that are in commerce. Accordingly, the U.S. Environmental Protection Agency's Office of Research and Development (EPA/ORD) is working to transform its exposure research portfolio to achieve a vision that provides chemical exposure foresight for thousands of chemicals at a time in an efficient and timely fashion. This vision recognizes regulatory needs for exposure screening, prioritization, and timely decision-making to manage the vast number of existing unevaluated chemicals along with new chemical registration applications. Furthermore, this vision will position exposure science to enable chemical management priorities related to environmental justice and cumulative impacts assessment and for a future of sustainability and environmental, social, and economic prosperity whereby exposure foresight is applied in a "green chemistry context" to inform chemical design and use (NAS, 2022; Anastas et al., 2021; Ganesh et al., 2021).

EPA/ORD's computational research employs and further develops New Approach Methods (NAMs) for exposure to equip regulatory partners with state-of-the-art tools to support chemical safety decisions (Kavlock et al., 2018; Wambaugh et al., 2019). The stakes are high for public health and the environment due to the need to balance societal

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interests for chemical production and protection. Chemistry, engineering, and manufacturing play a large and critically beneficial role in the modern economy and society for disease prevention (e.g., Serafini et al 2020), food security (e.g., Popp et al 2013), and enhancing human well-being (e.g., Matlin & Abegaz, 2011). The chemical sector makes up a sizeable portion of the U.S. economy estimated at $5.2 trillion, representing 25 % of the U.S. Gross Domestic Product (GDP), and supporting 4.1 million jobs (NAS, 2022). Even so, the U.S. ranks third behind the European Union and China in chemical sales (The European Chemical Industry Facts and Figures, 2023). These beneficial interests need to be managed while also considering the threat that chemical pollution poses to ecosystems (Saaristo et al., 2018), biodiversity (Groh et al., 2022), environmental justice communities (Mah, 2016) and public health (Landrigan et al., 2018; Naidu et al., 2021; Rappaport, 2016), and a habitable planet (Rockström et al., 2009, 2023; Persson et al., 2022; Cousins et al., 2022). Although these consequences tend to be studied separately, there is growing appreciation for a one-health perspective that considers their interconnectedness (Prata et al., 2021).

EPA has various regulatory authorities for managing chemical environmental risks, e.g., Toxic Substances Control Act (Wilson and Schwarzman, 2009). Similarly, the European Union manages chemical risks under its Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) program (Williams et al., 2009) and more recently by establishing an assessment framework for 'safe and sustainable by design' chemicals and materials. Under these programs, Fantke et al., 2022, and Bruinen de Bruin et al., 2022 describe a supporting exposure science strategy. Chemical manufacturing in China has burgeoned over the last 20 years and has been associated with accidental releases resulting in increased regulation (e.g., "Law on Hazardous Chemical Safety of PRC") (Wang et al., 2018). Considering the scale of chemical production, management requires transparent, systematic, timely, evidence-based decisions where computational approaches provide the only practical means of success.

To support these high stakes public policy decisions, computational exposure research must account for inherent complexities of chemical exposure. Exposure is a multifaceted phenomenon that spans diverse and intertwined domains of chemical, biological, physical, and social sciences traditionally represented as a continuum from source to dose and ultimately effect (Lioy, 2010). This traditional depiction ignores the compounded complexity of an exposure reality that encompasses an enormous and dynamic anthropogenic chemical space where little or no information is available for the vast majority of chemicals. The traditional exposure continuum represents one dimension of computational exposure science with the second dimension being one of enormous and highly diverse chemical space and the computational tools needed to integrate and process these dimensions efficiently and credibly. This complexity is well exemplified by the human and ecology health-relevant diverse range of chemicals in consumer products that numbers in the tens of thousands (Dionisio et al., 2018) with exposure to chemicals from near- and far-field sources occuring via multiple pathways, and with a strong social/behavioral determinant (Stanfield et al., 2021). The true number of chemicals and transformation products to which humans are exposed is unknown but likely is in the hundreds of thousands considering global trade and chemicals in commerce (Grulke et al., 2019; Wang et al., 2020). As such, EPA's computational exposure science is evolving and includes the Exposure Forecasting (ExpoCast) program that was initiated in 2009 (Kavlock and Dix, 2010) to complement Toxicity Forecasting (ToxCast) in providing screening-level, high-throughput predictions to support next-generation risk assessment methods (Cohen Hubal et al., 2010; NRC, 2007, 2012; Egeghy et al., 2016; Wambaugh et al., 2019). This evolution has been leveraged by complementary computational exposure research occurring outside the Agency including the work of Csiszar et al., 2016 and Jolliet et al., 2021.

Scientific, public health, and regulatory interests strongly align in the continued development and advancement of computational exposure science (Vandenberg et al., 2023). Interests and research development efforts parallel those of computational toxicology (Thomas et al., 2019). The objective of this article is to provide: 1) our strategic research themes for advancing computational exposure science; 2) an overview of accomplishments; and 3) research plans extending over the next 5 years. Our working definition of computational exposure science incorporates three defining characteristics: predictive, rapid (e.g., conducted in hours or days rather than months or years), and high-throughput (e.g., considers thousands or tens of thousands of chemicals). These characteristics allow the Agency to assess exposure more comprehensively and at a pace and scale proportionate to the realities with which chemicals are placed in commerce with potential for release.

2. Computational exposure science at the cutting edge

The research themes defining the cutting edge of exposure science represent an evolution of the traditional elements of methods development, measurements, and models described a few decades ago (Ott, 1990). Technological advances in analytical instrumentation, data availability, and computing together with the maturation of machine learning algorithms, have transformed these elements into their computational equivalents.

There are three broad strategic themes to EPA's computational exposure research program: 1) chemical data curation; 2) data acquisition and integration, including the application of measurement methods employing non-targeted analysis; and 3) model development. Complementing and cutting across these scientific advances are efforts to make the research readily useable to decision makers and the public, explicitly quantifying uncertainty, providing transparency, and ensuring reproducibility. There is an order to these efforts with chemical data curation serving a "core" role, feeding into data development efforts and ultimately culminating in models that deliver high-throughput exposure predictions (Fig. 1). We provide below an overview description of EPA's research advances on these fronts and future plans, followed by a case study related to chemicals in consumer products to illustrate application, integration, and policy relevance.

2.1. Chemical data curation

Exposure science relating to chemicals relies upon knowledge of chemicals and associated properties that define interactions occurring across physical, environmental, and biological systems. Hence, a high-quality database of chemical substances, structures, and associated

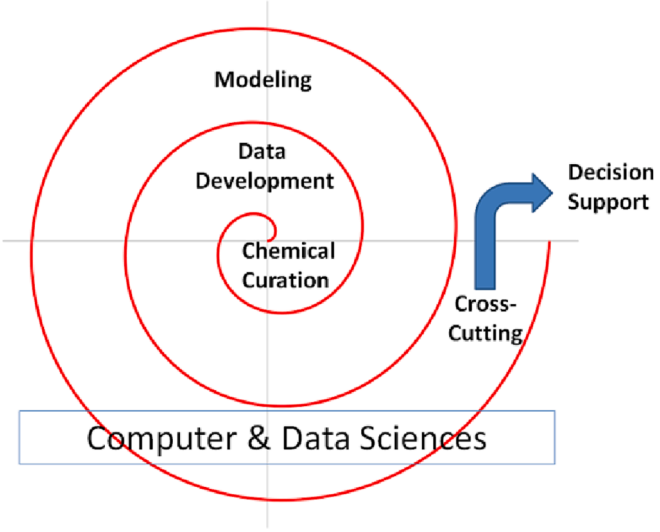

Fig. 1. Major components of computational exposure research program and their relation to one another.

data, supported by chemical curation and enabling accurate property and data associations, is foundational to research in computational exposure and toxicology (Thomas et al., 2019). There are three defining characteristics of this effort: 1) a comprehensive accounting of the anthropogenic environmental chemical landscape; 2) high-level confidence in the accuracy with which each chemical, structure, and related meta data are specified; and 3) integration and accessibility of chemical lists and associated data for use in computational modeling, decision support, and as a public resource.

EPA's Distributed Structure-Searchable Toxicity (DSSTox) chemical database project launched over 20 years ago with the goal of providing curated, high-quality structure-data associations to support predictive modeling in toxicology (Richard and Williams, 2002; Grulke et al., 2019). In the intervening decades, the database has expanded considerably to over 1.2 million substances (Grulke et al., 2019; Williams et al., 2017). DSSTox represents one of the highest quality sources of chemical substance and structure linked to exposure-related data. It has grown to be one of the most comprehensive collections of substances of anthropogenic origin potentially released to the environment. It includes chemicals from across a wide range of source categories with potential for environmental release or exposure (e.g., industrial, consumer products, food packaging, pharmaceuticals, biosolids) and includes environmental degradants and metabolites. Critical to its success has been the attention to ensuring quality associations of chemical identifiers (such as Chemical Abstract Services Registry Numbers–CAS-RN, chemical names, and structures) to corresponding data and chemical lists. Inconsistencies in chemical identifiers and errors in chemical-data associations, which propagate through models, are pervasive across public internet chemical resources (Williams et al., 2017). In contrast, the close coupling of expert manual curation with automated quality checks, and a strict enforcement of 1:1:1 mappings of CAS-RN, chemical name, and structure to a unique substance ID (DTXSID), sets the DSSTox project apart (Grulke et al., 2019). This focus on quality chemical substance annotations and data associations is essential to the foundational role DSSTox plays in supporting computational exposure and toxicology research and downstream modeling efforts. Plans over the next 5 years are to continue curating DSSTox records for chemicals and lists, as well as expand curation of chemical relationships (e.g., for parent compounds, metabolites, and transformation products) and chemical groupings of importance to EPA's program offices and researchers (e.g., per/polyfluorinated alkyl substances, or PFAS). In addition, there will be increased focus on registration of polymers, mixtures, and ill-defined substances, adding more detailed annotation and linkages to defined structure substances, as well as on emerging contaminants identified through non-targeted analysis (NTA). This work will be accomplished using existing strategies and processes that have been successful in achieving the current listing (Grulke et al., 2019).

The DSSTox chemical substance database underpins EPA's CompTox Chemicals Dashboard (hereafter referred to as "Dashboard"; Williams et al., 2017), where chemical structures and associated identifiers serve as primary integrators of multiple data streams also supported in the Dashboard. The Dashboard provides a portal to a wide range of chemical lists (currently $>$ 420) spanning regulatory, chemical use, literature, and structure-based groupings. Chemical identifiers input into the batch search enables download of related content, including structures, predicted properties, toxicity, bioactivity data, and list associations (Lowe and Williams, 2021). The Dashboard also provides access to a wide range of chemical substance-linked resources and tools within EPA and across the Internet. The Dashboard provides uniformity and specificity in the representation of chemicals and serves a critical linking function across measurements, data development, and modeling research efforts. We expect exposure-relevant curation and linkages to continue to expand over the next 5 years meeting the needs of EPA program offices as exemplified by recent efforts related to biosolids (Richman et al., 2022) and organohalogen flame retardants (Bevington et al., 2022).

2.2. Acquisition and integration of exposure-relevant data

The data requirements for assessing chemical environmental exposures reflect its complexity in spanning chemical, physical, biological, environmental, and social sciences. These sciences all factor into the source to dose continuum conceptual framework representing exposure science (Fig. 2). The complexity represented here is magnified by an exposure-relevant chemical landscape that is very large, poorly characterized, and of widely varying properties.

Our data development efforts are strongly integrated with modeling. Data form the basis of model development and models inform data collection needs. Data streams are being developed in a manner consistent with recommendations for standardized organizing infrastructures that support increasing useability and accessibility of data (NAS, 2018). Our efforts are employing informatics, data mining, and data infrastructure technologies to support collection, organization, and integration of existing and emerging exposure data streams. These efforts are increasing the volume, quality, and accessibility of exposure-relevant data while enhancing the reproducibility and defensibility of the risk-based decisions they support allowing the rapid incorporation of new data into decision support frameworks and tools. Finally, these efforts enable the development of machine-learning models for filling gaps for data-poor chemicals. The data streams across the exposure continuum are depicted in Fig. 2 and described below.

2.2.1. Chemical source and release

Quantitative estimates of the amount of chemicals released or emitted from near-field or far-field sources is a key driver of receptor exposure (Arnot et al., 2012; Isaacs et al., 2014). Sources are generally classified in two ways: 1) commercial sector use, i.e., consumer, industrial, or agricultural; and 2) proximity to the receptor, i.e., near-field or far-field (Jayjock et al., 2009). Consumer product releases drive near-field (indoor) exposures as well as serve as a source for down-the-drain and out-the-window flows and are informed by quantitative information on chemical concentrations in products and chemical emission processes (e.g., release from articles or the releases from the use of consumer products). Over the last decade, we have focused efforts on the consumer product source category. This has included the curation of chemical ingredients in consumer products developed from public documents and classified by use (Dionisio et al., 2015, 2018; Goldsmith et al., 2014). These data have been used as a basis for estimating median population human exposure (Isaacs et al., 2014; Wambaugh et al., 2014; Ring et al., 2019). Future work is planned that will address two important data gaps: 1) the application of computational exposure strategies to access data poor chemical exposures occurring within the workplace (Minucci et al., 2023); and 2) chemical exposures that result from consumer articles such as furnishings and building materials.

There are far-field source data gaps associated with specific facilities, unique industrial processes, and agricultural applications. Current approaches rely on very crude surrogates such as production volume (Arnot et al., 2012; Ring et al., 2019) and property-based partitioning into compartments of release. To address this data need, we are developing approaches that use chemical function to inform releases (Li et al., 2021). Furthermore, we are working to develop models that will integrate available release information and downstream monitoring data (e.g., air or water) to develop quantitative estimates of loadings into different environmental compartments. Data models and databases that organize release information from different sources (Meyer et al., 2020) will be expanded to include predicted releases and integrated with chemical curation workflows as was done for surface water in Sayre et al., 2022.

2.2.2. Chemical fate and transport

Fate and transport are governed by chemical properties and environmental conditions. Data that characterize both the residential/indoor and outdoor environments are needed for characterizing

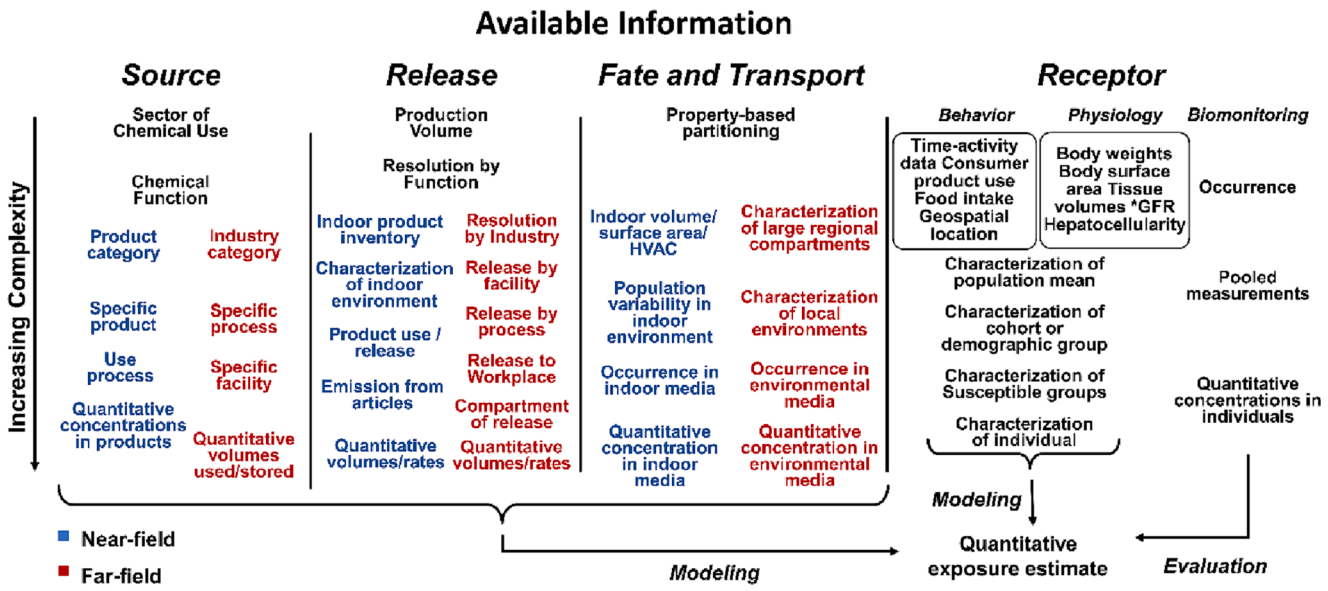

Fig. 2. Varying complexity in exposure-relevant data streams. The simplest data may be very general, while more detailed data may be specifically relevant to near-field and far-field exposure sources. Data availability dictates for which exposure pathways, exposure scenarios, and populations defensible exposure predictions can be developed. *GFR = Glomerular Filtration Rate.

movement and ultimate partitioning of chemicals. Environmental monitoring data provide the gold-standard fate information for use in assessments and for evaluating models of chemical fate and transport. There exist dozens of potentially relevant environmental media including ambient and indoor air, soil, surface-, ground-. waste-, and drinking- water, food, biosolids, precipitation, house dust, and sediment. We have made a major advance in support of fate and transport characterization and modeling by developing a harmonized database comprised of large amounts of monitoring data linked to media and chemical identifiers (Isaacs et al., 2022).

2.2.3. Human receptors

Human exposure is influenced by both behaviors and physiology. Behavioral information captures receptor activities that impact what sources, releases, and contaminated environmental media are encountered. This includes time-activity data that quantifies time spent in different microenvironments (McCurdy et al., 2000), exposure-relevant microactivities (e.g., bathing, smoking), food and drinking water intakes (Vieux et al., 2020), and consumer product use patterns (Isaacs et al., 2014). These consumer and household "habits and practices" data quantify the use of consumer products (e.g., detergent, paint, disinfectants) within the home including the nature and frequency of use, as well as the possession of furnishings, consumer articles, or building materials relevant to indoor sources (e.g., vinyl flooring or wallcoverings, foam-containing furniture, large electronics). These data traditionally come from cross-sectional surveys that can be expensive and quickly become dated. There is a recognized need to acquire data that are more dynamic and contemporary such as information inferred from social media or alternative "big data" sources (Ben et al., 2019). Physiological information is required to quantify exposure intakes (such as those impacted by breathing rates), assess their magnitudes relative to body weight or body surface areas, and predict fate and transport of chemicals within the body (i.e., toxicokinetics). Data relevant to understanding variability in absorption, distribution, metabolism, and elimination (ADME) of chemicals (and thus ultimate tissue concentrations) include tissue or organ volumes and blood flows, glomerular filtration rate (GFR), hepatocellularity, and cytochrome P450 enzyme expression (Wetmore et al., 2014).

2.2.4. Emerging technologies and data sources

The previous sections specify multiple domains along the source-to-dose continuum for which critical data gaps continue to exist. To address these gaps, we are developing and employing new informatic, computational, and analytical tools to support the collection and organization of exposure relevant data, as well as sustainable infrastructures for providing these data to the public and decision-makers. This includes informatics tools for identifying, extracting, and curating data from public documents including innovative literature retrieval systems (Baker et al., 2018) and sustainable applications for document management, data curation (Mansouri et al., 2016), and quality tracking. Non-traditional survey instruments take advantage of smart-phone technology and "the quantified self" to provide data related to consumer habits and practices (Von Goetz, N et al., 2018) activity patterns (Straczkiewicz et al., 2021), or microactivities (Myslín et al., 2013). In addition, other non-traditional data streams such as consumer product purchase information are being used to augment traditional field- or panel-study information on behavior (Tornero-Velez et al., 2021; Stanfield et al., 2021). Advanced/emerging monitoring technologies include sensor technologies (Peltier and Buckley, 2020) and non-targeted analysis (see below) that provide expanded capabilities for individual-based measurements and for the measurement of much larger chemical space, respectively. Machine learning methods are being used for data extrapolation and read-across using available chemical-specific property, use, and structure descriptors to fill gaps for thousands of data-poor chemicals. Lastly, sustainable data infrastructure and delivery systems such as the Dashboard will continue to be developed so that data are readily accessible to stakeholders in a timely, transparent, and usable manner.

2.2.5. Measurement at a scale of chemical exposure reality

High-resolution mass spectrometry (HRMS) and NTA methods are providing cutting-edge measurement capabilities that are enabling advances in computational exposure science. NTA methods rely on HRMS to rapidly acquire data on thousands of molecular features and then implement sophisticated workflows to assign likely chemical structures. These methods are cutting-edge in two ways: 1) the measurable chemical space is on par with the number of anthropogenic chemicals present in products and the environment; and 2) it is possible to detect chemicals without a priori knowledge of their presence in a sample or the

availability of a standard (Guo et al., 2020). NTA provides a means to reveal the vast unknown of chemical environmental contaminants suggested by Landrigan et al., 2018, and expand interdependent quantitative modelling (Sobus et al., 2018). Examples of NTA applications and impact include chemical surveillance and discovery in house dust (Rager et al., 2016; Panagopoulos Abrahamsson et al., 2021), drinking water (Newton et al., 2018), consumer and personal care products (Phillips et al., 2018), recycled materials (Lowe et al., 2021a), human biological samples (Chao et al., 2022), and PFAS source attribution (Washington et al., 2020). Building on these successes, efforts are now being made toward applications for disaster and emergency response (Phillips et al., 2022).

The application of NTA to computational exposure science is constrained by technical challenges to broad adoption. Technical challenges stem from a lack of standardized methods and tools for performing NTA studies, as well as a lack of available training resources for lab personnel that are new to NTA. Indeed, successful NTA projects require combined expertise in analytical chemistry, HRMS, cheminformatics, and data processing/statistical analysis procedures. We are therefore developing and evaluating tools to overcome these constraints thereby enabling broader adoption of NTA by Agency clients and partners. This includes the development of HRMS reference data for the universe of anthropogenic chemicals and their degradants potentially present in the environment. DSSTox supports this activity by containing: 1) a growing inventory of curated chemical substances; 2) MS-ready structure (McEachran et al., 2018) mappings between registered substances and measurable (via HRMS) structures; and 3) metadata to help prioritize chemical candidates (McEachran et al., 2017) including predicted in-silico spectra and prevalence on chemical lists such as ExpoCast and ToxCast (McEachran et al., 2019). Chemistry web applications, such as the Dashboard, allow easy access to these data through advanced batch and structure searching capabilities. Future developments will include the aggregation and harmonization of public domain experimental spectra generated within the agency or provided by collaborators. The Dashboard provides access to tools that aid in chemical identification (McEachran et al., 2020) based on the method of analysis (Lowe et al., 2021b) and retention time indices (Aalizadeh et al., 2021). DSSTox content is being expanded to enable NTA application to PFAS measurement as a chemical class of interest to many stakeholders (Williams et al., 2022). It is further being developed to support collaboration with other researchers who are developing specialized tools for chemical identification (e.g., FluoroMatch described in Koelmel et al., 2022).

The need for standard or consensus NTA methods is being addressed through EPA/ORD's Non-Targeted Analysis Collaborative Trial (ENTACT), which was initiated to characterize differences across laboratories, identify best practices, and harmonize approaches (Ulrich et al., 2019). ENTACT prompted an international collaborative workgroup called Benchmarking and Publications for Non-Targeted Analysis (BP4NTA) (Place et al., 2021). The BP4NTA workgroup is a part of the cutting-edge effort in promoting and coordinating NTA efforts across government, academia, and industry thereby accelerating the pace with which standardized NTA methods are developed and adopted (Peter et al., 2021; Fisher et al., 2022; see resources at https://nontargetedanalysis.org/).

NTA is central to our computational exposure science efforts in identifying understudied or previously unknown chemicals in products and environmental and biological media at a scale comparable to chemicals in commerce. Advances are being made in mapping the relevant chemical space to various NTA methods (Black et al., 2022). In the next 5 years, we plan to expand NTA in multiple ways including: 1) development of methods to support quantitative non-targeted analysis (qNTA) and procedures for estimating quantitative uncertainty, building on the work of McCord et al., 2022 and Groff et al., 2022; and 2) expansion of NTA laboratory capabilities through technology transfer to state and regional stakeholders greatly extending chemical monitoring efforts supporting local public health interests. The availability of quantitative NTA and associated methodologies and tools is necessary for NTA to be fully utilized within a risk assessment context. This is important because risk assessment underlies the mission of many government laboratories. Because NTA encompasses a large and data-poor chemical space, the computational exposure science methods described here are necessary and relevant. Accordingly, there is a synergy and interdependence between between qNTA and computational exposure science methods in support of risk assessment.

2.3. Development of high throughput exposure models

Modeling takes on critical importance for computational exposure science as it is the only practical means by which chemical exposures across an inherently large and poorly characterized chemical space can be estimated. Although exposure modeling is a well-established field with a long history (Jayjock et al., 2007), high-throughput exposure (HTE) model development efforts have largely occurred only over the past decade. There are three defining characteristics to HTE models and derived estimates: 1) large numbers of chemicals, i.e., ten-to-hundreds of thousands; 2) data-poor chemicals; and 3) greater uncertainty relative to traditional modeling approaches making them more suitable for screening or prioritization (Csiszar et al., 2016; Jolliet et al., 2021; Arnot et al., 2006; Isaacs et al., 2014; Wambaugh et al., 2013). As illustrated in Fig. 3, data requirements are partially dictated by the complexity and specificity of the needed predictions. HTE models trade precision for capacity (Wetmore et al., 2015; Sipes et al., 2017; Ring et al., 2017). For appropriate decision-making contexts such as prioritization, we aim to tailor the complexity of the models to the granularity of the application (e.g., days vs. hours or individuals vs. average population) and the availability of data to parameterize that model. The quantification of uncertainty is a key consideration in model development and application and is discussed as a cross-cutting issue below.

Computational exposure modeling has made enormous progress relying on the National Health and Nutrition Examination Survey (NHANES) biomonitoring data in an approach termed the Systematic Empirical Evaluation of Models (SEEM). This approach has been used to estimate exposure for nearly 8,000 chemicals based on data from 106 NHANES biomarkers (Wambaugh et al., 2014) and again more recently using a model ensemble approach to screen exposure for nearly 700,000 chemicals (Ring et al., 2019). This current version of the SEEM framework incorporates multiple predictors of exposure, including HT models for consumer (Isaacs et al., 2014; Shin et al., 2017; Li et al., 2018) and far-field pathways (Arnot et al., 2012). However, the current version does not take location into account or address specific cohorts and has limitations in how existing exposure predictors are extrapolated to data-poor chemicals. Research is underway to address these limitations as well as to identify and characterize exposure pathways and chemicals outside the domain of the current model. In addition to these updates to the SEEM framework, research will address the need for geospatial resolution in HTE models such as the Stochastic Human Exposure and Dose Simulation High Throughput (SHEDS-HT) model, to allow for the integration of population and/or spatial variability in near-field and far-field sources as Wodtke et al. (2022) have recently shown to be important.

2.3.1. High throughput toxicokinetics

A primary application of computational exposure science is for the purpose of exposure screening or prioritization requiring comparison to the target dose that results in biological activity or toxicity. This comparison is achieved through toxicokinetic modelling. Chemical-specific toxicokinetic data are unavailable for most chemicals in commerce (Bell et al., 2018) although this is beginning to change as *in vitro* assays are developed to characterize key aspects of toxicokinetics (Rotroff et al., 2010; Breen et al., 2021a). Over the past decade, an extensive library of chemical-specific *in vitro* measurements has been developed for chemicals in commerce and the environment (Wetmore et al., 2012;

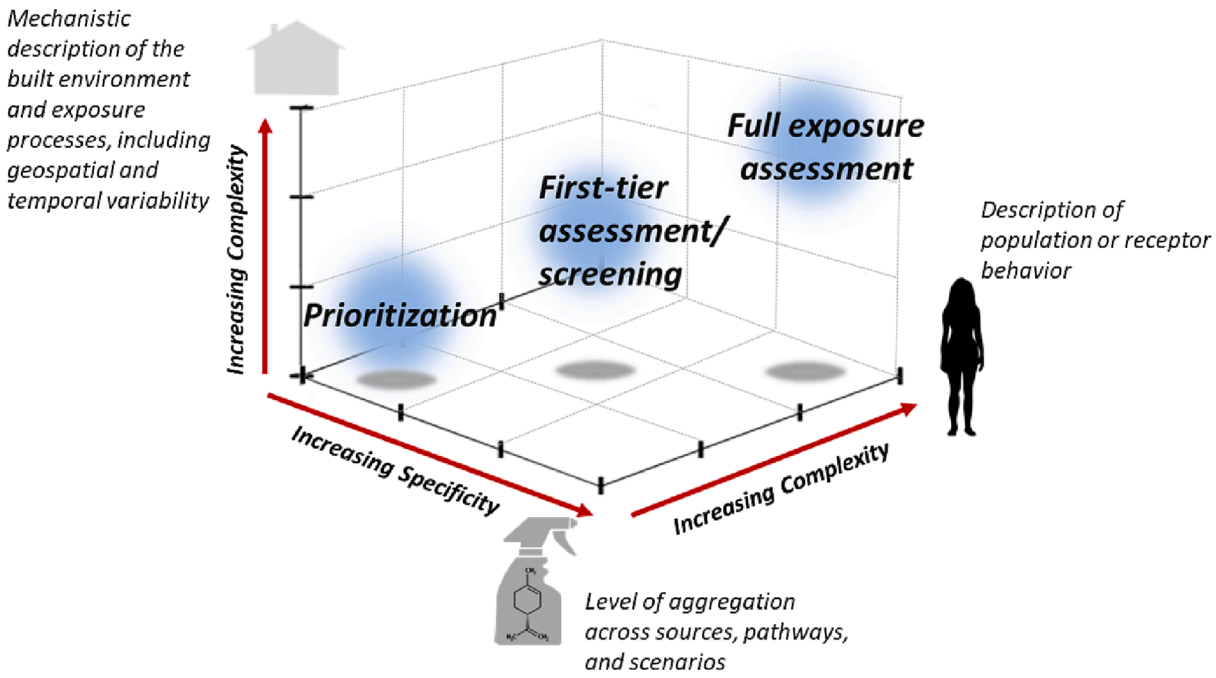

Fig. 3. Fit-for-purpose exposure models. As decision contexts move from priority-setting to screening to exposure assessment, descriptions of receptors and the built environment become more complex, while the level of aggregation of exposures may decrease, with all potential exposures considered in prioritization, whereas specific statute-based scenarios are considered in full assessments.

Paini et al., 2019). Generic (chemical independent) toxicokinetic models have been developed for use with *in vitro* toxicokinetic data to couple exposure predictions with *in vitro* screening data (Wetmore et al., 2015; Breen et al., 2021b). These models aim to cover key routes of exposure (Linakis et al., 2020) and can include key aspects of population variability in physiological processes that drive toxicokinetics (Ring et al., 2017). Future research will build on work of Ring et al., 2017 with an emphasis on reducing key sources of model uncertainty (e.g., route specific bioavailability, restricted vs. non-restricted clearance) and evaluating variability within sensitive or highly exposed populations including those occupationally exposed.

2.3.2. *Integration of data and models*

Models and measurements are intertwined and iterative. We build and evaluate models based on what we can measure, make models to predict what we cannot measure, and generate measurements for what we cannot model. The more chemical space covered by measured data, the more model predictions can be made. The simpler the model, the easier it is to get chemical-specific data, e.g., Wambaugh et al., 2014. The importance of near-field sources to HTE modeling (Wambaugh et al., 2013) led to new, high-throughput consumer exposure models including SHEDS-HT (Isaacs et al.,2014), Ex-Priori (Hubbard et al., 2022), and RAIDAR-ICE (Li et al., 2018) as well as monitoring databases (Dionisio et al., 2018). The availability of the extensive DSSTox chemical structure database coupled with new structure-based models for predicting physio-chemical properties (Mansouri et al., 2018, 2019) accessed from the Dashboard, led to the third generation SEEM model making predictions of general population daily intake rate for nearly half a million chemical structures (Ring et al., 2019).

Human exposure is highly dynamic. However, the available data and models used to represent exposure tend to be static and incremental so that model estimates lag contemporary reality by years or decades. Recognizing trade-offs of uncertainty, duration, and cost of chemical assessments (Hagiwara et al., 2022), our research efforts optimize workflow efficiency related to aggregation, curation, and harmonization of data inputs into model runs. For example, improved approaches for the extraction, harmonization and curation of data have been developed (Mansouri et al., 2016) and are being used to extract physiochemical property data from public domain resources. A model registration system and workflow managing the relevant aspects of modeling are being developed to include: 1) automated splitting of training and test sets; 2) standardized description and methodology for generation of descriptors; and 3) automated approaches to make new predictions with an appropriate model version.

Workflows to integrate exposure data and model predictions into decision-making for risk assessment are also critical. We are actively developing workflows to integrate exposure information with hazard/toxicity information for risk-related decision-making. Efforts include the Public Information Curation and Synthesis (PICS) workflow for chemical prioritization under TSCA (US EPA, 2021) and RapidTox workflows for decision-making in contexts including emergency response (Mumtaz et al., 2021). In the next five years, we plan to continue the development of these workflows for high-priority applications of risk-related decision-making, including: 1) a workflow for the rapid evaluation of potential hazards and exposures to children and women of child-bearing age using Toxicity Estimation Software Tool (T.E.S.T.); 2) an application of NTA as part of a multi-omics evaluation of exposure and health; 3) workflows specific to the process of evaluating exposure potential for new chemicals under TSCA; 4) exposure scenarios of regulatory interest including occupational exposures and aggregate exposures within specific locations or demographic groups believed to be at risk; and 5) workflows developed in collaboration with EPA's Office of Water for risk screening of chemical contaminants in biosolids.

2.4. *Cross-cutting considerations*

The elements making up computational exposure science described above all constitute lines of quantitative evidence. The goal is to develop and provide this quantitative evidence in a way that informs transparent, reproducible decision-making in rapid, predictive, and health-protective risk assessment (NAS, 2017). This goal requires quantitative evaluation of uncertainty and variability in both measured data and model predictions. It also requires publicly available software tools so that analysis workflows can be integrated and reproduced. Finally, it

involves scientific review and effective communication about the data, models, and software tools to enable decision-makers to use them easily and confidently. These considerations are adopted from computational toxicology as described in Thomas et al., 2019 and more recently van der Zalm et al., 2022.

Data development tools are being designed for transparency, reproducibility, and flexibility. These tools collate data and meta data from available non-standardized, widely varying formats, applying transparent, reproducible workflows to clean, standardize, and harmonize the data format. This is achieved while maintaining a clear "chain of custody" back to the original data (i.e., no destructive editing). Furthermore, a link to the original reporting context is maintained. In the next five years, we plan to expand and refine our existing data informatics and infrastructure tools for curation, data development, and modeling as described above. Network modeling is of particular interest as an approach to relate and link heterogeneous data streams. In all applications, data architecture will be carefully designed for transparency, reproducibility, and flexibility, and planned for ultimate integration with existing tools such as the Dashboard.

Transparent quantification of uncertainty and variability is a key consideration in model development efforts. The capture and transparent portrayal of uncertainty and variability is a key consideration in model development efforts. This is accomplished by forward propagation of uncertainty and variability in model parameters to predictions using a Monte Carlo approach where estimates are derived by trying different randomly sampled combinations of parameters to map out a range of possible solutions (Bauer, 1958). Examples include SHEDS-HT (Isaacs et al., 2014), and HTTK-Pop (Ring et al., 2017; Breen et al., 2022). For model parameter values derived from data, uncertainty is estimated using statistical modeling approaches. For example, median population exposures and their 95 % credible intervals are inferred from urine biomonitoring data using Bayesian methods (Stanfield et al., 2022). Bayesian methods refer to inferring distributions of plausible parameter values that are consistent with available data and prior assumptions (Eddy, 2004). Uncertainty in toxicokinetic parameters estimated from a database of in vivo concentration vs. time data (CvTdb) is quantified using meta-regression methods where disparate but potentially informative sources of information are combined to derive a consensus model to determine a range of plausible answers or predictions (Van Houwelingen et al., 2002; Sayre et al., 2020; Wambaugh et al., 2019a). Transparency and reproducibility are achieved by publishing model and analysis code in peer-reviewed papers (Groff et al., 2022; Ring et al., 2019), on GitHub, and on platform-specific repositories such as the Comprehensive R Archive Network (CRAN). Furthermore, we plan to build on existing work to apply statistical modeling to estimate uncertainty and evaluate confidence in NTA and toxicokinetic results.

Our research delivery is consistent with FAIR principles (Findability, Accessibility, Interoperability, and Reuse of digital assets; Wilkinson et al., 2016). Data and models, as well as examples for use and descriptions of their development and functionality, are downloadable via EPA's website (https://www.epa.gov/chemical-research/downloadable-computational-toxicology-data), hosted on figshare, GitHub, CRAN, and other easily accessible sites. An increasing amount of data is also available for incorporation in models via our APIs (https://api-ccte.epa.gov/docs/index.html). Development of research products is tailored toward maximizing data for multiple uses, in part by adopting widely available terminology ontologies such as the UMLS Metathesaurus, which links millions of terms and term relationships (Bodenreider, 2004).

Despite compelling justification for the need of computational exposure science and enormous progress in its advancement, there remain substantive challenges to adoption within a risk management decision context. These challenges fall into three general and related categories: 1) chemicals tend to enter the regulatory pipeline one at a time favoring traditional exposure assessment approaches; 2) there is appreciable inertia that needs to be overcome and associated lag in adoption and incorporation of new computational tools and data resources into existing decision work flows; and 3) the need to develop data science expertise within organizations responsible for risk management decisions facilitating the adoption and use of computational exposure tools and data resources within existing decision workflows.

3. Chemicals in consumer products case study

We have chosen the consumer pathway based on its relative importance among exposure pathways and the diversity of relevant chemicals. We highlight propylparaben (PP) as an example to show the relevance and integration of research strategy elements across a variety of efforts. PP is a preservative found in many water-based cosmetics including creams, lotions, shampoos, and bath products. It is also used as a food additive. It functions as an antifungal and antimicrobial agent. PP is currently being evaluated for endocrine receptor activity under EPA's Endocrine Disruptor Screening Program and has been included on the TSCA Workplan for existing chemicals. Unambiguous chemical identification is fundamental to efforts to evaluate exposure. Chemicals in consumer products were initially identified by mining publicly available Material Safety Data Sheets (MSDS) from a large consumer product retailer where 1,797 unique chemicals in 8,921 products were identified (Goldsmith et al., 2014). The database was further developed and expanded to include >20,000 unique chemicals from >61,000 consumer products (Dionisio et al., 2018; Williams 2017). These data complement European efforts to inventory chemicals in cosmetics (n = 2,878; 2006, Decision 2006/257/EC). In CPDat V3, data for PP was curated from 805 public documents, reflecting 1040 different products in 79 unique product categories. Products that were reported to contain PP included 65 categories of personal care products (including many cosmetics), several arts and crafts products (e.g., adhesives), children's products (e.g., bubble solution) as well as air fresheners, carpet and floor cleaners, and pet products.

NTA of consumer products made with virgin and recycled materials (Phillips et al., 2018; Lowe et al., 2021) identified PP even in products for which it was not reported by the manufacturer, including paper products, fabric products, and plastic children's toys. This demonstrated the utility of NTA in augmenting reported ingredient information. Future research is planned to analyze larger samples of representative products with greater potential for human and ecological exposures.

The chemical curation effort of mapping chemicals to products addresses a fundamental need by establishing the near-field source term for source-to-dose models. The next key data needs for the consumer product scenario relates to better identification of those who are purchasing and using specific consumer products and a better understanding of their "habits and practices" when using the products. We have evaluated demographic patterns of product use through access to nationally representative longitudinal market research data (Tornero-Velez et al., 2021). Further, by linking products with the chemicals they contain via DSSTox, we evaluated chemical co-exposures, and highly exposed subpopulations (Stanfield et al., 2021). This analysis identified PP as the second most prevalent endocrine-active chemical brought into homes via purchased consumer products. PP is also a key component of chemical combinations whose prevalence varied by population group. These results informed the selection of PP-containing mixtures for novel *in vitro* toxicity testing of mixtures. A data mining approach similar to that used in the Nielsen analyses has been applied to NHANES biomonitoring data to identify demographic patterns of co-exposure to consumer product-related chemicals (Kapraun et al., 2017). In that analysis, PP was not only found to co-occur with other parabens among at least a third of the U.S. population, but the prevalence of the combinations varied by demographic group. As both Nielsen and NHANES data lag current exposures by several years, we are exploring a dynamic data pipeline for contemporary product use information relying on publicly available social media such as Google Trends search data.

Quantitative data on chemical concentrations in environmental or biological media have also been curated and harmonized within the Multimedia Monitoring Database (Isaacs et al. 2022). Monitoring input has included NTA to identify consumer product chemicals in residential environmental media including dust, air, and drinking water. In MMDB, PP concentrations were reported in several media including surface water and fish, as well as human urine, blood, breastmilk, and amniotic fluid.

Research advances relating to modeling chemicals in consumer products includes the development of a HTE model for consumer pathways (SHEDS-HT, Isaacs et al., 2014) and integration of SHEDS-HT and other HT consumer models into consensus aggregate exposure predictions within the Systematic Empirical Evaluation of Models (SEEM) framework for thousands of chemicals (Ring et al., 2019). SHEDS-HT was parameterized with the quantitative data from CPDat for over 1000 chemicals to generate SEEM exposure predictions. PP was one of 114 chemicals with available NHANES biomonitoring data that enabled calibration of the SEEM model estimates (mg/kg-BW/day intake of chemical) and quantification of uncertainty. Plans to expand and improve SEEM predictions includes the application of machine learning for extrapolating existing consumer exposure predictions from SHEDS-HT to data-poor chemical-product combinations and integration with NTA to improve characterization of consumer exposure sources. Ultimately this work can support identification of priority chemical mixtures for risk evaluation and the characterization of unique exposure sources among sensitive or underrepresented populations building on the work of Tornero-Velez et al., 2021 and Kapraun et al., 2017.

A principal goal of these efforts is to provide EPA regulators and other stakeholders with timely, transparent, and credible exposure-related information to support evaluations or management decisions concerning chemicals used in consumer products. Examples include data extraction, curation, and measurement efforts related to chemicals in children's consumer products supporting chemical pre-prioritization under TSCA, and evaluation of chemicals under the Minnesota Department of Health's (MDH) Toxic Free Kids' program (https://www.health.state.mn.us/communities/environment/childenvhealth/tfka/reports.html). These resources have also been used to score nominees for the MDH Chemicals of Emerging Concern (CEC) initiative (Isaacs et al., 2023) and have been used in collaborative efforts to support the identification and prioritization of breast-cancer related chemicals for further study based on mixture exposure potential (Koval et al., 2022). Other collaborative efforts include the use of Quantitative Structure Use Relationship (QSUR) models to support the development of a comprehensive inventory of flame-retardant chemicals to support assessments by the Consumer Product Safety Commission (Bevington et al., 2022). At the same time, chemical manufacturers are using computational exposure modeling approaches for evaluating risk to consumers and workers from exposure to mixtures (Sauer et al., 2020) and informing formulation decisions (Sunger et al., 2020).

4. Conclusions

There are numerous challenges to managing chemical risks within modern society. In the U.S. and across the globe, there are many historical examples of lapses resulting in harms to human health and the environment that became apparent after the fact and after great cost to public health had occurred (e.g., lead, asbestos, dichlorodiphenyltrichloroethane (DDT), polychlorinated biphenyls (PCBs), and the ozone destroying chlorofluorocarbons) (Landrigan et al., 2018). A critical aspect of the challenge to chemical management is the enormous gap in available information relating to exposure, hazard, and risk within the timeframe of regulatory and commercialization decisions, especially considering the many thousands of chemicals that are already in commerce (Woodruff et al., 2023). EPA's computational exposure research complements its computational toxicology efforts and together are designed to substantively close this gap in information and time. There are three strategic components to this program including chemical curation, data development, and modeling. Further, the data and tools developed follow FAIR principles (Findability, Accessibility, Interoperability, and Reuse of digital assets; Wilkinson et al., 2016) in being public, transparent, as well as tailored to EPA program office priorities and workflows for ready incorporation into management decisions. The resulting research is transformative toward achieving a goal of providing exposure foresight at a scale and within a timeframe commensurate with chemicals being placed in commerce and human and ecological receptors exposed. This research provides a critical piece to the environmental health puzzle that is needed not only to protect human health and the environment, but to address environmental injustice (Landrigan et al., 2018), "reinvent our relationship with planet Earth," and "become effective stewards of the global commons — the climate, ice, land, ocean, freshwater, forests, soils, and rich diversity of life that regulate the state of the planet and combine to create a unique and harmonious life-support system" (NAS, 2021).

Author contributions

The manuscript was written by TJB with contributions from co-authors related to their area of expertise. All authors have given approval to the final version of the manuscript. All authors contributed equally in providing draft material for various sections and edits throughout.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: On behalf of my coauthors and I, I hereby declare that we have no competing financial or personal relationship conflicts of interest that would bias the research presented in our article "Cutting-Edge Computational Chemical Exposure Research at the U.S. Environmental Protection Agency."

Data availability

No data were used for the research described in the article.

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