NEW JERSEY DEPARTMENT OF ENVIRONMENTAL PROTECTION

SCIENCE ADVISORY BOARD

FINAL REPORT

Approaches for Addressing Drinking Water and Wastewater Contaminants of Emerging Concern (CECs) in a Broader Context: Identification, Ranking and Treatment Removal

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Acronyms and Abbreviations used in this report:

AF: Adjustment Factor
API: active pharmaceutical ingredient
BAT: best available treatment
CEC: contaminants of emerging concern
DWQI: Drinking Water Quality Institute
EOHSI: Environmental and Occupational Health Sciences Institute
FDA: Food and Drug Administration [Appendix A]
GAC: granular activated carbon
GC: gas chromatography
GCITMS: gas chromatography with ion trap and mass spectrometry
HPLC: high performance liquid chromatography
LC: liquid chromatography
LD50: lethal dose to 50% of exposed organisms
LTD: lowest therapeutic dose
LOD: limit of detection
MCL: Maximum Contaminant Level
METIS: METIS is a chemical informatic platform built on open-source software that provides access to an aggregated database and estimation tool set focused on environmental fate and persistence parameters. METIS retrieves and assembles information from over 1,400 publicly available databases.
MS: mass spectrometry
NJDEP: New Jersey Department of Environmental Protection
NJDOH: New Jersey Department of Health
NJIT: New Jersey Institute of Technology
ng/L: nanograms per liter (parts per trillion, ppt)
PFAS: per- and polyfluoroalkyl substances
PPB: parts per billion
PPCP: pharmaceuticals and personal care products
PPT: parts per trillion
PQL: Practical Quantitation Level.
PRoTEGE: ProTEGE is an analysis and modeling platform that facilitates exposure calculations at multiple tiers, utilizing available data on a number of parameters.
QSAR: quantitative structure-activity relationship
RfD: Reference Dose
RO: reverse osmosis

RSC: Relative Source Contribution
SAB: Science Advisory Board
SOCs: synthetic organic compounds
TIC: tentatively identified compound
TTC: Threshold of Toxicological Concern
µg/L: micrograms per liter (ppb)
UF: Uncertainty Factor
USEPA: United States Environmental Protection Agency
USGS: United State Geological Survey
VOC: volatile organic chemical
WSV: Water Screening Value

INTRODUCTION:

Key terms

There is a need to clarify the distinctions between key terms ("terms of art") that are used throughout this report. Therefore, specific definitions are articulated as follows:

- *Contaminants of emerging concern (CECs)* can include both unregulated compounds with known identities (individually and as classes) and tentatively identified compounds (TICs).
- *Tentatively identified compounds (TICs)* are compounds that are detected by an analytical technique (e.g. gas chromatography-mass spectrometry [GC-MS] or liquid chromatography-mass spectrometry [LC-MS]) whose identity and concentration cannot be confirmed without further analytical investigation. It is recognized that current analytical methods do exist that can identify individual TICs. When an individual TIC is identified with defined confidence, it would then become an unregulated compound with known identity (see Appendix B).

Overview:

The members of the New Jersey Department of Environmental Protection (NJDEP) Science Advisory Board Committee on Contaminants of Emerging Concern in Water (CEC SAB) recognize that most CECs detected in the New Jersey's waters are not unique to NJ but are generally detected regionally and likely worldwide throughout the water use and reuse cycle. A subset of these CECs is persistent and mobile in environment media, contributing to their widespread detection in ground and surface waters, including sources of drinking water. Examination of databases and reports developed by other countries (Sweden, Germany), international organizations (United Nations, European Union) and other U.S. states can be useful in identifying potential CECs of interest here in New Jersey. The CEC SAB members are in agreement that the current chemical-by-chemical approach for developing drinking water standards (Maximum Contaminant Levels; MCLs) and water quality standards has tremendous rigor, as required by the regulatory process. As discussed in this report, even limited data from certain specific types of health effects studies can indicate the potential for significant concern and may warrant the development of a health-based drinking water guidelines. However, this approach is highly labor intensive for those CECs that have sufficient relevant data. Additionally, there may be insufficient data for a chemical-specific approach for other CECs, and MCL development is not feasible for the large number of CECs that can be detected using current analytical techniques. Therefore, there is a need to develop a prioritization scheme that could be used to select which classes of compounds and CECs may pose the greatest hazards. An underlying goal is finding cost effective methods that can interrupt or decrease the pathways resulting in human exposures to levels believed to pose little or no public health concern.

One recommendation is the establishment and codification of a CEC working group that would cut across disciplines and interested parties representing government, private sector and academia. Although this working group could be initially established by the NJDEP, its codification by the legislature would create a group to specifically address CECs and make recommendations to the NJDEP/New Jersey Department of Health (NJDOH) and possibly the New Jersey Drinking Water Quality Institute (DWQI). A dynamic database incorporating peer-reviewed literature and data compiled by the state is needed to identify and address CECs of greatest concern. A targeted approach to develop and fund innovative research efforts would enable the state to keep abreast of CECs and protect public health.

The CEC SAB committee formed three workgroups (Toxicology, Analytical Methods, and Treatment Technologies) to develop reports (Appendices A, B and C, respectively) on aspects of the charge questions relevant to each of these three areas. Additionally, a case study on considerations for grouping and addressing per- and polyfluoroalkyl substance (PFAS) based on common toxicity and/or removal by the same treatment technology is presented in Appendix D.

The Toxicology Subgroup discussed methods that could be used to prioritize regulatory investigation from among the large number of chemicals currently used in commerce and new chemicals being developed. It is important that any approach that is developed incorporate a ranking hierarchy that would allow for hazard assessment, chemical monitoring and potential treatment options that may be useful across chemical classes. The hazard assessment should rely on exhaustive literature reviews that are continuously updated by the staff of the NJDEP Environmental Research Library, ongoing monitoring and establishment of a CEC working group to make informed assessments. The introduction of new use compounds or alternatives to currently used compounds for large scale production or commercial uses should be examined for their potential impact, and monitoring to observe trends in concentration and occurrence data should be conducted over multiple years.

The examination of the critical properties (Figure 1), as well as exploration of quantitative structure-activity relationships (QSAR) and data-rich computational tools such as NJRisk (Georgopoulos and Mueller, 2019) and the USEPA CompTox Chemistry Dashboard at https://comptox.epa.gov/dashboard (Williams et al., 2017), can provide initial information on CECs of interest in New Jersey. It should be noted that the information provided by each of these tools differs in some aspects; a detailed comparison of NJRisk and the USEPA CompTox Chemical Dashboard is presented in Appendix E. For example, the Risk Ranking function in NJRisk provides relative impact rankings for CECs, as described for in the earlier NJDEP SAB report on CECs (NJDEP SAB, 2012a; 2012b), and these rankings would be useful in prioritizing a list of contaminants for more detailed evaluation. In contrast, the USEPA Chemistry Dashboard does not include such a function, but it provides more quantitative information relevant for human health risk assessment (e.g. available toxicity values) than NJRisk.

Additionally, the USEPA Chemistry Dashboard is also curated, can help identify surrogate chemicals and can perform literature searches.

While it is recognized that there will be both false positives and false negatives when utilizing these approaches, these computational resources provide initial information that can be clarified through further investigation. It is recommended that NJDEP researchers develop expertise in using these approaches to establish screening levels, and that they provide feedback on their usefulness and ways for improvement as prioritization and screening tools. However, it must be emphasized that these methods are not appropriate for use as the basis of regulatory values at this time.

The Analytical Subgroup discussed the methods that can be employed for initial detection of both unregulated compounds and TICs and for further identification and quantification of compounds of interest. The analytical group at the Rutgers Environmental and Occupational Health Sciences Institute (EOHSI) has previously worked with State of New Jersey organizations to develop analytical methods for drinking water and surface water. NJDEP, in collaboration with EOHSI, the NJDOH analytical laboratory and the United States Geological Survey (USGS), should expand on earlier efforts (NJDEP, 2003) to identify TICs and then develop reasonable detection guidance values with the goal of applying those values to treatment recommendations for community water systems. TICs are non-target analytes and are often present in a sample at or below 1 ppb range. Tentative identification of many of the TICs present is based on library matches, and their relative abundance within a sample can be estimated as a first step followed by a more in-depth chemical identification approach.

Groupings of compounds can be made based on criteria such as: commercial use (e.g. pharmaceutical, personal care product, petroleum product), chemical properties, naturally occurring vs. synthetic and others. Some of the compound groups (e.g. pharmaceuticals, personal care products, petroleum products) can be further subdivided into chemicals with similar toxicological modes of action (e.g. pharmaceutical classes such as non-steroidal anti-inflammatories, steroids, etc.). This approach has been utilized in evaluating contaminants detected in surface waters by the USGS (Bexfield et al., 2019; Bradley et. al., 2017), and it could be an initial approach taken for unregulated compounds, including TICs. The ability to detect and identify unknowns continues to improve dramatically, with the introduction of more reasonably priced high-resolution mass spectrometric instrumentation. The approach using a molecular formula, derived from an accurate mass, has been used as the basis for proposed standardization in reporting confidence of the identification of unknown compounds (Schymanski et. al. 2014). Tentative identification of an unknown is supported by accurate measurement of mass fragments and searches of ever-expanding commercial libraries with software using accurate mass for structure prediction. The highest degree of confidence is described as confirmatory analysis of an analytical standard on the same instrument using the same operating conditions. Identification with a considerable degree of confidence, however, is

now often possible in the absence of such a standard. For future work on CECs, there needs to be close collaboration between the analytical chemists and treatment experts in the development of appropriate indicator compounds for both analytical purposes and treatment analysis, since many of the same chemical properties influence both analytical identification and treatment approaches.

The Treatment Technology Subgroup focused on treatment systems for removing CECs from source water for potable use and from effluent water quality for point source discharge. CECs often originate from wastewater treatment plants, and the ability to treat these contaminants with existing processes is challenging at the observed concentrations. Drinking water treatment plants face similar or possibly even greater challenges.

The subgroup considered several approaches to address CECs in the two types of plants including:

1. Using indicator compounds to potentially represent the vast array of CECs that are observed throughout the water cycle. With representative indicator compounds, analytical requirements could be reduced, potentially allowing for better tracking and identification of the most effective treatment processes. However, using indicator compounds to represent a large group of CECs may lead to underestimating potential breakthrough or formation of transformation products that may be more toxic than the parent compound. Thus even with treatment, toxicity including carcinogenicity and/or mutagenicity may still be of concern.

2. Requiring specific treatment technology to address CEC removal. With this approach, issues include the nature of the contaminants that are present, the presence of mixtures of CECs and/or other constituents, variability in CECs present in influent, plant capacity/footprint, capital and operating costs, existing processes that are in place, and the potential to impact further innovation of novel treatment technology.

3. Measuring and monitoring the toxicity and/or mutagenicity of wastewater treatment plant effluents and raw and/or finished drinking water using *in vivo* and/or *in vitro* methods across toxicological endpoints to support innovative treatment technology. Enhancement of the current methods and monitoring techniques for these toxicological endpoints and/or development of new methods is needed to improve the ability to evaluate potential public health impacts. The development and implementation of these approaches would require additional research and investment.

While the third approach based on toxicological evaluation may be the most scientifically sound for detecting changes in the composition of waste streams that are of potential human health

concern, significant technical work would be needed to develop such approaches for routine use especially in a wastewater treatment facility. Therefore, using all three approaches may be necessary.

Conducting a Life-Cycle Analysis for a class of chemicals and examining where interventions can be made to reduce chemical escape/breakthrough into the environment can reduce the amount being released and minimize the volume of contaminated media that ultimately needs to be treated. Incorporating more closed loop processing with recapture technology would prevent or reduce off-site contamination. Often the costs of cleaning up contaminated media are not borne by the producer of the product, but rather are allocated to those using the resource downstream. In addition to the potential human health effects that are the focus of this report, discharge of wastewater containing CECs can also cause adverse ecological effects. Therefore, it is critical that technologies are incorporated at the source of the CEC discharge to receiving waters to reduce the distribution of the CECs and the need for treatment by downstream WWTP and drinking water treatment plants. The public health and ecological costs are often not factored into production and operating costs when conducting a traditional Life-Cycle Analysis. The assumption that both the watershed and the airshed will dilute the contaminant to below levels of human health and ecological concern has proven to be a fallacy, and there is a need to prevent discharge or treat at the earliest point possible. The entity that discharges the CEC (including the parent compound and/or transformation products) during manufacture or use should take responsibility for the compound's liability and costs for remediation or removal. How such costs can be passed on to the entity making or using the CEC is beyond the scope of this report.

RESPONSES TO CHARGE QUESTIONS

Part I:

- **Are there approaches for evaluating water contaminants of emerging concern (CECs) in a broader context, to supplement the current chemical-by-chemical approach for development of MCLs and water quality standards?**

Historically, most drinking water standards have been based on human health risk assessments of specific chemicals, most often using data from laboratory animal studies although several standards are based on human epidemiological findings. Exceptions to the focus on specific chemicals in drinking water regulation include the treatment-oriented regimen for disinfection byproducts (DBPs). DBPs occur as complex mixtures in drinking water, and routine analytical methods measure only a small number of the many DBPs that may be present. Toxicological data needed for quantitative risk assessment are available for only a few DBPs, some of which are carcinogenic in laboratory animals and are associated with increased cancer risk in human epidemiology studies. However, it is not feasible to regulate some DBPs at their health-based levels, especially for the carcinogens, due to the public health benefits of disinfection. Therefore,

the MCLs for DBPs are based on a treatment-based level for group of DBPs (trihalomethanes and haloacetic acids) that have toxicological data and can be routinely analyzed. Various treatment methods were instituted to reduce the substrates (e.g. organic compounds from naturally occurring plant material) that result in formation of DBPs during water treatment. Other methods were employed to manage source water and reduce DBP production in the distribution system. The occurrence of other chemicals or families of chemicals in drinking water may also be reduced through augmented treatment and source water management approaches. For examples, volatile organic contaminants (VOCs) could be addressed as a group by using air stripping or GAC as long as it is designed for the most difficult CEC to remove.

Chemicals with minimal toxicological information represent a problem in risk assessment and risk management, including when they occur in drinking water. In 2004, NJDEP published a "Discussion paper to generate dialogue on several approaches for reducing unregulated synthetic organic contamination from public drinking water supplies (NJDEP, 2004)". This paper discussed two options for addressing unregulated contaminants, one based on assessment of toxicity data and another based on analytical and treatment considerations. NJDEP (2004) discussed that the approach based on toxicity considerations could involve grouping chemicals based on common toxicity, with carcinogenicity given as the example, but it was noted that this approach was unlikely be effective since there is little or no health effects information for many newly identified contaminants in NJ drinking water. A later review entitled "Future Challenges to Protecting Public Health from Drinking Water Contaminants" by Rutgers and NJDEP scientists (Murphy et al., 2012) includes a discussion of potential approaches for toxicity assessment and risk prioritization of large numbers of unregulated drinking water contaminants. The approaches reviewed include high throughput toxicity testing of large numbers of individual contaminants for prioritization and toxicity testing of concentrates of complex mixtures of drinking water contaminants. Currently, these approaches may be useful for screening purposes, but they do not provide the data that are needed to develop numerical drinking water guidelines. Additionally, these approaches are still being developed, and technical issues related to both the procedures used to conduct the assays and the interpretation of the results must be resolved before they can be used for routine toxicity screening. However, with the advancement of *in vitro* testing approaches for some specific endpoints such as cell proliferation, gene expression, endocrine receptor activity and many others, prioritization based on a biological assessment of these endpoints is now becoming feasible. These high throughput approaches to examine specific mechanisms of action are being developed at the national level, and their results can be employed in evaluation of CECs at the state level. Research into which approaches may be the most useful will depend on the classes of compounds known or suspected to be present in the water.

The second toxicity-related option proposed in NJDEP (2004) is based on "generic" standards for individual and total concentrations of contaminants in a certain class (e.g. synthetic organic compounds; SOCs) that lack sufficient health effects information for development of chemical-specific values. NJDEP currently uses such an approach in groundwater standards based on

generic values for SOCs with or without evidence of carcinogenicity, when there is insufficient data to develop a chemical-specific value. A disadvantage of such an approach is that the levels at which contaminants within a group (e.g. SOCs) cause health effects vary over orders of magnitude.

General approaches that have been devised to assess potential toxicity of contaminants with little or no toxicological data were reviewed by the SAB panel. These include: development of a surrogate Reference Dose (RfD) that falls below the great majority of RfDs for other contaminants in the same general toxicological category, estimation of a chronic NOAEL and RfD by applying factors to the LD_{50} or subacute NOAEL, development of thresholds of toxicological concern (TTCs) based on structural alerts and basic toxicology data, evaluations based on QSAR, and specific approaches for evaluation of active pharmaceutical ingredients (APIs). These approaches are described in detail in Appendix A. As is the case for the approaches discussed above, these approaches may be useful for screening and prioritization purposes, but they do not provide the data needed to develop numerical drinking water guidelines for regulatory purposes.

Another potential approach involves the use of computer programs (Machine Assisted Learning/Artificial Intelligence) designed to search and rank chemical information obtained from toxicological/chemical databases that incorporate multiple endpoints to assist in making informed decisions concerning whether a new compound or set of compounds may pose a risk to human health or the environment. NJRisk (Georgopoulos and Mueller, 2019) and the USEPA Chemical Dashboard (Williams et al., 2017) are examples of such computational tools. As new information is added the predictive ability of these tools increases. Such tools are valuable, but again, interpretation of the information that they provide requires a group of experts that cuts across disciplines. This is another reason for establishing a panel of experts to assess and make decisions on CEC rankings. It is essential that tools such as NJRisk and the USEPA Chemical Dashboard be constantly updated based on new information appearing in the literature and incorporation of high throughput toxicity testing data that is being generated by governmental agencies. These models can be run very quickly, and it can be rapidly determined if the potential risk has increased or decreased with consideration of the new data. This database mining approach is currently used across the chemical and pharmaceutical industries for risk determinations generally similar to those that would be done for emerging water contaminants.

Again, it must be emphasized that the approaches discussed in Appendix A and the Machine Assisted Learning approach cannot be relied upon without incorporating into the loop a group of experts whose scientific knowledge and judgement will help to interpret the results and assess the potential risk. As one example, while there may be limited data on the specific compound being evaluated, it may be possible to relate it to a structurally similar compound or to other compounds that interact with the same receptor based on experts' knowledge and supported by peer-reviewed literature. The relative affinity of the target receptor for these types of compounds could be used for establishing a ranking. This type of approach has been employed with

estrogenic activity as the basis for assessing potential endocrine disruption across classes of compounds.

As discussed in more detail in Appendix A, the approaches described in this report are not designed or intended to be used to provide definitive estimates of risk. Rather, it is recommended that they be considered when providing treatment advice to affected water systems, in setting priorities for the derivation of new health-based guidance values, in setting priorities for new or improved laboratory analytical methods, in selecting contaminants for future monitoring studies, and in assisting in the evaluation of water quality.

An important question when implementing the approaches discussed above is how to consider the risks of multiple chemicals that are present in an environmental medium. Potential approaches for evaluating the risks of multiple chemicals that co-occur, either from the same chemical class or from different chemical classes, are discussed in the response to the next charge question.

Finally, analytical considerations related to identifying and evaluating emerging contaminants individually and in groups must be considered. These considerations are discussed in Appendix B.

The answer to the charge question is: Yes, there are methods that can be employed to address CECs in a broader context, but there needs to be better integration across current and evolving approaches to capture the relative risks for individual compounds, as well as mixtures (discussed below). No single approach can be relied upon without incorporating into the loop a group of experts whose scientific knowledge and judgement can help to interpret the results and assess the potential risk and benefits. Adequate human and monetary resources need to be provided to expand upon the initial work carried out over the past decade(s) on this topic. As discussed in the response to second charge question below, addition of appropriate treatment can greatly reduce CECs in both drinking water and other source waters.

- **Can unregulated drinking water and/or wastewater contaminants be grouped and addressed based on common toxicity and/or removal by the same treatment technology?**

From a toxicological point of view, when large classes of compounds with similar chemical structures are known to act through a well-defined mechanism of action (e.g. activation of a specific receptor), their risks can be evaluated to a certain extent based on their interaction and activation of the target receptor compared to other related compounds. For example, the toxicological potency of acetylcholinesterase inhibitors can be compared because of their common effect on acetylcholine activity that impairs nervous system function. The use of toxic equivalency factors (TEFs) based on specific biological activities can be scaled to broader sets of compounds, although there may be other effects or factors unrelated to the basis of the TEFs that may alter the toxicity for a given member of the class.

The TEF approach has been employed with polychlorinated biphenyls and substituted dioxins and furans, based on their relative potency for activation of the aryl hydrocarbon (AH) receptor which is known to be a major factor in their relative toxicity. In this approach, a biological ranking for compounds in the class is established based on comparison with the activity of the most active known compound in the class. If multiple compounds in the same chemical class are present, it is assumed that the TEQ (toxic equivalent; TEF x dose) from individual compounds are additive. This assumes that toxicity occurs through the same mechanism of action or target receptor for all compounds in the class, while noting that the toxicodynamics of this group of compounds do vary depending on whether you are dealing with mammals including humans, avian species, or teleosts, resulting in slightly different TEFs for each of these groups. This is due to the differences between mammals, birds, and fish in affinity of the AH receptor for the different congeners. As with the acetylcholinesterase inhibitors described above, this type of an approach can be used when a known receptor or mechanism of action is identified.

This approach has been used to assess the potential toxicity of complex mixtures of compounds in these classes. It is most definitive when it is based on the internal doses of the compounds within an organism. It has also been applied to assessing the human toxicity of mixtures of these chemicals in external exposure matrices (e.g. fish tissue, soil or sediment). However, it is important to be aware that the biological impacts that determine the TEFs relate to the internal dose-effect relationship, and many factors can modify the compounds' availability for uptake into the body from external exposure matrices. The bioavailability and toxicokinetics (absorption, distribution, metabolism, and excretion) will also differ among members of the chemical class, and these parameters are affected by factors related to both the exposure matrix and the specific chemical. Therefore, these uncertainties must be noted when TEFs are applied to concentrations of contaminants in exposure matrices such as fish tissue, soil, or sediment. The internal dose can be estimated using established pharmacokinetic computer models, and these estimates can be compared to concentrations that are known to be biologically active.

While estimating the toxicity of the chemical classes mentioned above is relatively straightforward, the difficulty that arises is that the number of compound classes being used in commerce is immense. Although the compounds of potential concern can be subdivided into large classes, there is no specific toxic endpoint or mechanism of action that can be used across all of the compounds, or even within most chemical classes of compounds. In addition to the uncertainties related to differences among chemical classes, the biological heterogeneity and the multiple pathways and redundancies built into maintaining the cellular or organism homeostasis can mask or alter dose response effects. Due to these biological factors, activation, inactivation or non-responsiveness of structurally similar chemicals is commonly observed. These concepts are illustrated by the case study of toxicological considerations for considering PFAS as a group (Appendix D).

When toxicity factors (Reference Doses [RfDs] for non-cancer effects and slope factors for cancer risk) are available, approaches have been developed for estimating the combined risks of multiple contaminants that co-occur in water or other media. For carcinogens that have slope

factors, the cancer risks of individual contaminants can be summed. For non-cancer effects, USEPA has developed an approach in which the Hazard Quotients (fractions of the RfD) of individual chemicals that affect the same target organ or organ system are added to determine a Hazard Index. A Hazard Index less than 1 (one) indicates that adverse effects are unlikely from chronic exposure. The Minnesota Department of Health (MDH) has developed an approach similar to the USEPA Hazard Index approach for a list of drinking water contaminants that have acute and/or chronic oral Reference Doses and drinking water guidelines. As with the USEPA Hazard Index approach, the cumulative risk of compounds known to impact similar organ systems that co-occur in drinking water can be estimated with a combined exposure index. Supporting information for this approach and a calculator that provides the exposure quotient for concentrations of contaminants found in drinking water is found on the MDH Human Health-Based Water Guidance Table webpage.

While an approach similar to the USEPA Hazard Index and the MDH calculator could be employed by NJDEP as a screening tool, it must be noted that such approaches do not distinguish among the different toxicological endpoints and modes of action that can be involved with toxicity in the same organ. If it is known that different contaminants cause toxicity in the same organ through differing modes of action, then strict additivity and dose-response equivalency for responses cannot be assumed. As stated above, this approach should only be used as a broad screening tool when deemed appropriate, and it is not appropriate for all groups of chemicals. For example, as described in Appendix D, this approach is not appropriate for all PFAS as a group, since there is evidence for different mechanisms of action for toxicity among some PFAS.

The advancements in treatment systems and approaches does allow for the removal of many CECs from both potable water and wastewater treatment. Table 1 (below) shows the ability of the various treatment regimens to remove selected classes of compounds. As shown in Table 1, effective treatments vary depending on the class of compounds being treated. It should also be noted that this table represents drinking water and that the source water characteristics can impact these relative efficiencies. The range of effectiveness within a group likely reflects the variability in physical-chemical characteristics among specific compound within the group. For the classes of synthetic organic compounds included in Table 1, both biological activated carbon (BAC) and reverse osmosis (RO) were the most consistently effective treatment processes. Zhang et al. (2017) used 16 indicator compounds to represent 11 classes of CECs in evaluating the effectiveness of BAC (also referred to as biologically active filters). Indicator compounds were selected based on their wide use, detection at significant frequency in the water cycle, persistence in the environment, recalcitrance to treatment, and representativeness of the vast array of CECs with respect to chemical properties. One of the unintended benefits of placing these treatments on drinking water plants to address regulated compounds is that other CECs, both known and unidentified, will also be effectively removed. Many or most of these treatment approaches are also applicable to wastewater, although their efficiency may be lower in this more complex matrix.

Table 1. Drinking Water Treatment Processes Used for CEC Removal[1,2]

Group	Class	AC	BAC	O_3/AOP	UV	Cl_2/ClO_2	Coagulation/ Flocculation	NF	RO	Degradation {B, PD, AS}
EDCs	Pesticides	F-E	E	L-E	E	P-E	P	G	E	{PD} - E
	Industrial Chemicals	E	E	F-G	E	P	P-L	E	E	{B} – G-E
	Steroids	E	E	E	E	E	P	G	E	{B} – L-E
	Fire Retardant	P-G	E	F-G			P			
	Metals	G	G	P	P	P	F-G	G	E	{B} - P, {AS} -E
	Inorganics	P-L	F	P	P	P	P	G	E	P-L
	Organo-metallics	G-E	G-E	L-E	F-G	P-F	P-L	G-E	E	L-E
	PAHs	F-E		L-E			P			
PhACs	Antibiotics	F-G	E	L-E	F-G	P-G	P-L	E	E	{B} - E
	Anti-depressants	G-E	G-E	L-E	F-G	P-F	P-L	G-E	E	G-E
	Analgesics		E				P-L			
	Anti-inflammatory	E	G-E	E	E	P-F	P	G-E	E	{B}- E
	Antiepileptic		E							
	Lipid regulators	E	E	E	F-G	P-F	P	G-E	E	{B} - P
	X-ray contrast media	G-E	G-E	L-E	F-G	P-F	P-L	G-E	E	{B and P}- E
	Psychiatric control	G-E	G-E	L-E	F-G	P-F	P-L	G-E	E	G-E
PCPs	Synthetic musks	G-E	G-E	L-E	E	P-F	P-L	G-E	E	{B}- E
	Sunscreens	G-E	G-E	L-E	F-G	P-F	P-L	G-E	E	G-E
	Anti-microbials	G-E	G-E	L-E	F-G	P-F	P-L	G-E	E	{B} - L-E
	Surfactants/ detergents	E	E	F-G	F-G	P	P-L	E	E	{B} - L-E

[1]References: Black & Veatch (2007). Axe and Dyksen (2020), Zhang et al. (2017). Zhang et al. (2016).

[2]EDCs – endocrine disrupting compounds; PhACs – pharmaceutically active compounds; PCPs – personal care products; AC – activated carbon; BAC – biologically activated carbon; O_3/AOP – ozone/advanced oxidation process; Cl2/ClO2- Chlorine/Hypochlorite; NF – nanofiltration; RO – reverse osmosis; B/P/AS - biodegradation/ photodegradation (solar)/activated sludge, UV – ultraviolet.

E - excellent (>90% removal)
G - good (70–90% removal)
F - fair (40–70% removal)
L - low (20–40% removal)
P - poor (<20% removal)

In summary: Yes, CECs can be segregated into large groups, subdivided into classes of compounds and even subdivided further based on physical/chemical criteria. It is recognized that adding additional treatment such as reverse osmosis (RO) or granular activated carbon (GAC) can greatly reduce the public's exposure to large classes of compounds, including contaminants that have been identified but are not regulated, TICs and compounds that have not even been detected, thereby reducing the public's risk of adverse effects. The treatment of drinking water with BAC and RO appear to be the most promising of the treatment regimens. Because of their effectiveness across the groups, these processes may be viable approaches for removing many non-monitored chemicals. The risk from regulated compounds, identified but unregulated compounds, TICs, and yet unidentified compounds would be dramatically reduced. It should be noted that both of these treatment technologies, particularly RO, can involve high capital and operating costs.

- **Is there valid reasoning that would support (in a basis and background) requiring/recommending additional treatment processes at public water systems in geographical areas known to be impacted by multiple unregulated contaminants?**

There is justification for recommending or requiring additional treatment for public water systems located in geographical areas known to be impacted by multiple unregulated contaminants when there is evidence that contaminants are present in the drinking water at levels that could potentially affect public health. The potential human health risk of multiple unregulated contaminants (identified and/or TICs) found in public water systems is often unknown, but water systems known to have elevated levels of CECs should have additional analytical evaluation. The number, types and levels of the identified unregulated compounds and TICs present will determine the need for further study and possible recommendation of additional treatment. Extracts of such drinking water can also be tested with *in vitro* and some *in vivo* assays to evaluate specific endpoints (cell toxicity, estrogenic/androgenic activity, mutagenicity). This toxicity-based approach is not feasible for routine use at the present time but might be employed in targeted heavily impacted areas. In the future, it may be possible to use the high throughput toxicity tests that are currently being developed to evaluate such concentrates for a variety of endpoints of toxicity. As stated above, the nature and concentration of the unregulated compounds and TICs could establish both the type and extent of recommended or required treatment.

Part II:

- **Which groups or types of chemicals, from the tens of thousands currently and previously used, should be the focus of attention regarding NJ water quality concerns?**

Occurrence data from New Jersey, as well as other U.S and worldwide locations, are critical for prioritization of emerging contaminants from a human exposure perspective. The USEPA Unregulated Contaminant Monitoring Rule (UCMR), as well as studies performed by other groups such as USGS, states and academia, provide valuable information on occurrence of unregulated contaminants in drinking water. Similarly, biomonitoring data from the Center for Disease Control's National Health and Nutrition Examination Survey (NHANES) and other groups, including state biomonitoring programs, provide valuable information on human exposures to environmental contaminants. Although the number of compounds assessed by UCMR and NHANES is limited in scope, other research studies using newer analytical methods can identify additional contaminants, including those initially considered to be TICs (i.e. do not have analytical standards), that may need follow-up.

While the hazard and exposure characterization scheme (Figure 1) recommended in this report is valuable for prioritization of unregulated drinking water contaminants, certain specific characteristics indicate that a contaminant should be flagged as being of especially high priority. Drinking water contaminants that are highly persistent in the environment and/or the human body should be of high priority for evaluation as contaminants of concern because of their potential to build up in the environment and/or the body. In general, any compound found in NJ drinking water or source water with a human half-life known to be greater than a few days or weeks should be of high priority, unless it has been designed to have a longer half-life for a beneficial use in treating a disease and is produced in small amounts. Additionally, compounds with evidence of specific toxicological effects including carcinogenicity, endocrine disruption, developmental toxicity, or low-dose effects of concern (e.g. neurotoxicity) should be of high priority (see Figure 1 below).

- **Can the SAB make additional recommendations on how to focus on specific groups or types of chemicals in NJ waters, to build on their prior CEC report?**

While unregulated contaminants including TICs were previously typically thought to be of concern only at concentrations above approximately 1 ppb (µg/L), we now know that the health-based drinking water levels for some of these contaminants is much lower, in the single to tens of ppt (ng/L) range. This is particularly true for contaminants whose toxicity results from interactions with specific receptors at very low concentrations and/or bioaccumulate in humans. The conceptual diagram (Figure 1) below illustrates key consideration in identifying contaminants or groups of contaminants of concern in NJ source waters. These include data on mass of material used, frequency and concentrations at which the contaminant is detected, biological kinetics (e.g. half-life), known or predicted toxicity, persistence in the environment, and extent of removal by current treatment processes. Additional criteria could be likely be developed in the future to improve this approach.

NJRisk is a valuable tool for initial evaluation of information on these considerations. It searches large numbers of databases for chemical-specific information (METIS and PRoTégé). However, the databases that it accesses have not necessarily been updated to include current information from the primary scientific literature, while other computational tools such as the USEPA Chemical Dashboard can perform literature searches. Therefore, information from NJRisk should be supplemented by information obtained through a search of the recent primary literature. As is the case for the other screening methods discussed above, a group of NJ experts with scientific knowledge and experience should work with the modeling groups from appropriate organizations to help expand the scope and interpretive/predictive capabilities of this tool. In assessing a chemical's potential for consideration there needs to be an integration of the NJRisk approach with the use and environmental occurrence information mentioned above.

Shown in Figure 1 below is a schematic depicting potential critical pieces of information (shown as vectors) that can be used in identifying and ranking CECs present in drinking water. This example is provided as a strawman for potential ranking, and other parameters that may be important in assessing the potential impact of the compound can be added. The specific criteria for the ranking would need to be further refined. This could be incorporated into NJRisk as a preliminary screening approach and could be used either for contaminants found in specific New Jersey localities or statewide.

The environmental persistence of a compound is determined by its chemical structure, which influences its movement through different media and its ability to undergo metabolism and non-biological degradation and transformation. Other parameters that influence migration through the environment could also likely be assessed. For example, compounds that have the potential to move over large distances would be of greater concern than those that have limited mobility across media unless there is a potential for exposure from an elevated concentration within a confined area. The physical/chemical properties also address general characteristics of classes of compounds (e.g. organic, inorganic, organometallic, polymer; acid, base, neutral, salt; volatile, semi volatile, water soluble, lipid soluble).

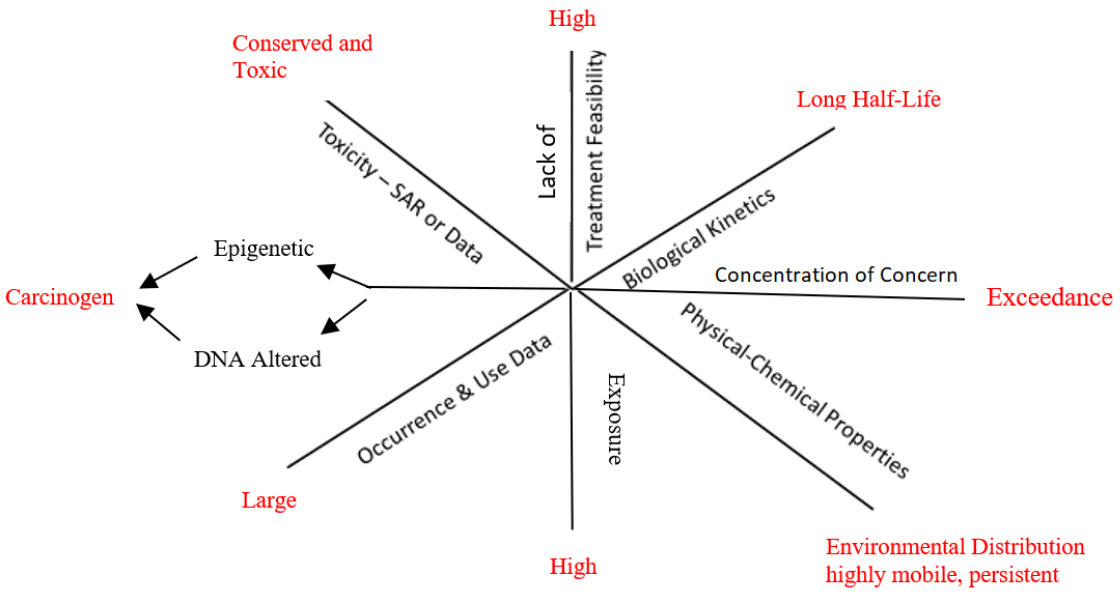

Figure 1. Important parameters represented by vectors for ranking of chemicals of concern.

While there needs to be discussion on how numerical ranking values could be derived, this approach, although simplistic, allows for ranking of CECs based on current scientific knowledge. If there are data gaps, then similar or related compounds can be assessed, or additional research could be carried out. In the case of PFOA (shown below), it is obvious for many reasons why this compound would warrant the concern that it has generated. As discussed in the detailed PFAS Case Study (Appendix D), it is recognized that the datasets for PFOA and several other PFAS compounds are quite robust and can allow for some differentiation among specific PFAS compounds. In the case of some of the short chain PFAS, the shorter half-lives, lower environmental concentrations relative to levels of concern, and other factors would likely rank these considerably lower than the PFOA. For many other PFAS, there are insufficient data to make an evaluation based on the parameters shown in Figure 1.

Using PFOA as a strawman for this type of an assessment, how might it look?

Vector Property	Parameter	Low 1-2	Mod. 3-4	High 5
1. Physical Chemical Properties (hydrophobicity, structure, persistence)	Environmental			5
2. Exposure	Human Tissue			5
3. Occurrence and Use Data	Production and use - Multiple Sources			5
4. Carcinogenic	Interaction with DNA	1		
	Epigenetic MOA		3	
5. Toxicity	Human & Animal Toxicity - multiple targets		4	
6. Biological Kinetics	Long half-life (years)			5
7. Concentration of Concern	NJ Health-based MCL is 14 ng/L; frequently detected, occasionally up to several 100 ng/L			5
8. Lack of Treatment Options	GAC, RO, ion exchange	1		

Summary Justification for Ranking:

1. Highly water soluble and does not bind well to soil matrices. Stable to degradation due to C-F bonds.

2. Present in human biomonitoring samples across NJ and the United States. Also reported in environmental receptors worldwide and in highly remote areas.

3. Large quantities were previously produced annually in the U.S. and utilized for many products. Production of large amounts continues overseas.

4. The compound does not interact directly with DNA itself, but secondary pathways lead to animal tumors; associated with increased cancer risk in humans. IARC (2016) lists as Group 2B

5. Mode of action for adverse effects involves activation of receptors at low exposure levels. Human epidemiology studies demonstrate effects on multiple organ systems, and internal doses (blood serum) levels are in the range of concern. Animal studies further support biological concerns. The compound has not been associated with human deaths from acute exposure.

6. The long half-life allows for accumulation to levels of concern in humans from very low levels of drinking water exposure.

7. The NJ Health-based MCL is 14 ng/L. (Concentrations of ≥1000 ng/L would be considered 1-2 range, 100-1000 ng/L would be 3, 20-100 ng/L would be 4, and <20 ng/L would be 5.) It is frequently detected in drinking water and source water above 14 ng/L, with some detections up to several 100 ng/L.

8. GAC, RO, and ion exhange have proven to be effective in removal of PFOA and other members of this class of chemicals to levels below detection and currently established New Jersey MCLs.

The panel that is recommended to be established for examining the CEC issues in New Jersey should consider and incorporate as appropriate previous work by New Jersey and other states that is based on peer-reviewed literature and other authoritative sources when addressing this issue in order to develop the best available approach for use in New Jersey. Such a tool then can be used in the process of ranking CECs or classes of CECs to determine which are of greatest concern.

Recommendations to NJDEP

- NJDEP should begin a pilot program to identify unregulated contaminants including TICs, and screening levels should be developed when possible, with the goal of applying those screening levels to treatment recommendations for community water systems. It is recommended that the approaches discussed in Appendix A, including TTC and LD_{50} approaches, QSAR/read-across methods and others, as well as NJRisk and the USEPA Chemical Dashboard chemical assessments, and novel approaches that may be hybrids of these, be explored for use in screening level development. These approaches should supplement the traditional risk assessment approach that can be used when sufficient health effects data are available. It is recommended that NJDEP toxicologists develop expertise in using these newer approaches to develop screening levels. This could potentially include evaluation by NJDEP toxicologists and other outside experts of possible approaches for grouping chemicals that have screening levels.
- Large classes of compounds that are known to be present in drinking water sources and surface waters in New Jersey and nationwide need to be examined, especially when a class of compounds is known to be widely used, frequently detected, persistent in the environment, and resistant to treatment; for example, pharmaceuticals, personal healthcare products, organophosphorus flame retardants and plasticizers, pesticides, metabolites (e.g., cotinine), and steroids are categories of some chemicals that potentially need to be monitored. While Appendix A reviews currently available *Risk Assessment Approaches to CECs with Limited Data*, these methodologies often rely on minimum therapeutic (or reference) dosages (when available), and may not have bearing on the wider population including sensitive populations.
- It is strongly recommended that a working group comprised of experts with appropriate scientific and engineering expertise from both within New Jersey state government and

outside of New Jersey state government be established to develop approaches for screening and ranking CECs or CEC classes, including use of the predictive tools mentioned in this report. At a minimum an *ad hoc* committee should be established to begin addressing these issues and establish workable procedures. This group should be formed as soon as possible. That being said, it is emphasized that results provided by these predictive tools, while useful for screening and prioritization, cannot be used as the basis for risk assessment (e.g. Reference Doses, drinking water guidance values) or development of regulatory standards. Therefore, other approaches for protecting drinking water need to be considered including the potential use of indicator compounds to represent the vast array of CECs being detected and observed. Furthermore, consideration of applying effective treatment technology for removing these indicator compounds is recommended. In the case when there is inadequate toxicity data to formulate a regulation or guidance value for a CEC that is of concern due to the frequency and levels at which it occurs and/or its persistence in the environment, then additional studies should be recommended. The data gaps need to be identified, and additional resources from both federal and state organizations with similar concerns could be a means to facilitate the necessary research. Both literature database searches and calls for information from the private sector could provide additional information. Depending on the extent of the data available, it may be possible to develop a guidance value. However, if there is not even enough data for this approach, the CEC could be fast-tracked to obtain minimal toxicological data. This may be in the form of a high throughput battery of tests to provide an initial indication of potential toxicological effects and potency. However, it must be noted that data from *in vitro* studies, including batteries of high-throughput assays, cannot be used as the basis for risk assessment (e.g. Reference Doses, drinking water guidance values) or regulatory standards under the current USEPA risk assessment guidelines that are used by New Jersey and other states.

Citations

Axe and Dyksen (2020). Supporting Information from paper in preparation. (Zhang, S, Gitungo, S, Axe, LB, Dyksen, JE, Raczko, RR Determining Indicator Compounds Representative of Contaminants of Emerging Concern in the Water Cycle, in preparation.)

Bexfield, L.M., Toccalino, P., Belitz, K., Foreman, W.T. and Furlong, E.; (2019). Hormones and pharmaceuticals in groundwater used as a source of drinking water across the United States Environ. Sci. & Technol. https://doi.org/10.1021/acs.est.8b05592

Black & Veatch (2007). Evaluation and Assessment of Organic Chemical Removal Technologies for New Jersey Drinking Water, Surface Water Report. Prepared for: NJDEP Division of Science, Research & Technology.
https://www.nj.gov/dep/dsr/dw/Black&VeatchSurfaceWater.pdf

Bradley, P.M. et. al., (2017). Expanded Target-Chemical Analysis Reveals Extensive Mixed-Organic-Contaminant Exposure in U.S. Streams. Environ. Sci. Technol. 51, 9, 4792-4802.

DWQI (2009). New Jersey Drinking Water Quality Institute. Hazardous Contaminants. https://www.state.nj.us/dep/watersupply/g_boards_dwqi_haz.html

Georgopoulos, P. and Mueller R. (2019). NJRisk: Development of an Integrated Computational Tool to Support Prioritization of Chemicals of Emerging Concern. https://nj.gov/dep/dsr/njrisk/NJRisk_RPS.pdf

Murphy, EA, Post, GB, Buckley, BT, Lippincott, RL, Robson, MG. (2012). Future Challenges to Protecting Public Health from Drinking-Water Contaminants. Annu. Rev. Public Health 33:209–24.

NJDEP (2003). New Jersey Department of Environmental Protection. The Characterization of Tentatively Identified Compounds (TICs) in Samples from Public Water Systems in New Jersey. Division of Science, Research and Technology Report. Prepared by: E. Murphy, B. Buckley, L. Lippincott, I. Yang, B. Rosen. https://www.state.nj.us/dep/dsr/TIC-report.pdf

NJDEP (2004). New Jersey Department of Environmental Protection. Opportunity for Public Comment on possible regulatory strategies to address the occurrence of unregulated organic contaminants in drinking water. Land Use Management, Water Supply Administration, Safe Drinking Water Program. February 2, 2004. Posted at https://www.nj.gov/dep/rules/ipr/ipr2004_0202sdw_paper.pdf

NJDEP SAB (2012a). New Jersey Department of Environmental Protection Science Advisory Board. Response to Charge Question on Contaminants of Emerging Concern. https://www.nj.gov/dep/sab/CECFramework%20Final%20Report.pdf

NJDEP SAB (2012b). New Jersey Department of Environmental Protection Science Advisory Board. Response to Charge Question on Contaminants of Emerging Concern. Appendix A: Final Workbook for Proposed CEC Framework. https://www.nj.gov/dep/sab/Appendix%20A_Final%20Workbook%20CEC%20Framework_August8_2012.pdf

Schymanski, E.L., Jeon, J., Gulde, R., Fenner, K., Ruff, M., Singer, H.P. and Hollender, J. (2014. Identifying small molecules via high resolution mass spectrometry: communicating confidence. *Environ. Sci. Technol.* 2014, 48, 4, 2097-2098

Williams, A.J., Grulke, C.M., Edwards, J. et al. (2017). The CompTox Chemistry Dashboard: a community data resource for environmental chemistry. J Cheminform 9, 61.

Zhang, S, Gitungo, S, Axe, LB, Dyksen, JE, Raczko, RR (2017) Biologically Active Filters – An Advanced Treatment Process for Contaminants of Emerging Concern, Water Research, 114, 31-41.

Zhang, S, Gitungo, S, Axe, LB, Dyksen, JE, Raczko, RR (2016) A Pilot Plant Study Using Conventional and Advanced Water Treatment Processes: Evaluating Removal Efficiency of Indicator Compounds Representative of Pharmaceuticals and Personal Care Products, *Water Research*, 105: 85-96.

Appendix A. NJDEP SAB CEC Committee Toxicology Workgroup

Risk Assessment Approaches to CECs with Limited Data

Background

Historically, most drinking water standards have been based on risk assessments of specific chemicals, using data from laboratory animal studies, though several are based on human epidemiological findings. Exceptions to the focus on specific chemicals in drinking water regulation include the treatment-oriented regimen for disinfection byproducts (DBPs). Only a small number of DBPs had been characterized toxicologically (which is still true), so the regulation of DBPs was instead based on the handful of characterized chemicals. Various treatment methods were instituted to reduce the substrates that result in production of DBPs during water treatment. Other methods were employed to manage source water and reduce DBP production in the distribution system. The occurrence of other chemicals or families of chemicals in drinking water may also be reduced through treatment and source water management approaches.

Methods for Chemicals with Limited Toxicological Data

Chemicals with minimal toxicological information represent a problem in risk assessment and risk management. There has been an effort to devise general approaches to address this paucity of data among organic chemicals. The Minnesota Department of Health (MDH) has developed methods that utilize the Percentile Approach, Lethal $Dose_{50}$ (LD50), and Threshold of Toxicological Concern (TTC), as discussed below:

One approach (the "Perecentile Approach") can best be described as an **examination of assembled panels of chemicals that do have toxicological data**. Typically, the chemicals that have data were placed into toxicological categories of carcinogen or non-carcinogen, endocrine disruptor, or cholinesterase inhibitor. The idea was to develop a value for the human dose or water concentration for these categories that was below the Reference Doses (RfDs) of the great majority (e.g. 95%) of the panel chemicals in that category. This value could be used as a surrogate RfD-like level, and a risk assessor would have a degree of assurance that the level would be health-protective.

Another approach, the **LD_{50} (lethal dose to 50% of exposed organisms) method**, involves dividing the oral LD_{50} by a factor of 17,000 to derive a value resembling a chronic effect No Observed Adverse Effect Level (NOAEL) and an additional factor of 100 to derive a value resembling a chronic effect RfD. Kramer et al. (1996) established the details of this method by examining 332 chemicals, half of which were pesticides and a quarter of which were solvents. The conversion factor of 17,000 represents the 95^{th} percentile of the distribution of the ratio of LD_{50} to the chronic NOAEL. A limitation of the LD_{50} approach is that effects from acute exposures that are intended to cause mortality are not necessarily relevant for predicting chronic

toxicity. Not surprisingly, the subacute NOAEL was a much better predictor of the chronic NOAEL, with a 95th percentile conversion factor of 87.

Another related approach for both carcinogens and non-carcinogens would be one of the versions of **Threshold of Toxicological Concern (TTC**), which was developed originally by FDA for food additives and contaminants. Essentially, it is a simplified method of using structural alerts (structural features of the molecule associated with certain types of toxicity), along with basic genotoxicity and mutagenicty testing data. In the subsequent refinement by Kroes et al. (2004), chemicals were assigned to three categories - typically carcinogens, non-mutagens with no structural alerts, and non-mutagens with a high median lethal dose (LD_{50}) and no structural alerts. A dose limit is assigned to each category based on a low (typically 5th) percentile chronic/subchronic No Observed Effect Levels (NOELs)/NOAELs of known characterized chemicals within that category. These serve in effect as the basis for crude "read-across" predictive modeling. Based on a panel of 730 chemicals and an uncertainty factor of 100, Kroes et al. (2004) assigned values of 0.025 µg/kg/day to carcinogens with structural alerts, 0.3 µg/kg/day to cholinesterase inhibitors and 1.5 µg/kg/day to chemicals with higher potential toxicity in the Cramer et al. (1978) Class 3. (The Munro et al. [1996] updated definitions of the Cramer classes 1, 2, and 3 are, respectively: simple chemical structure with known metabolic pathways and low toxicity end products; structure that is associated with more toxicity but lacking structural features of concern; structure suggesting even more toxicity and less safety.) These values were below the relevant RfDs for 95% of the chemicals in each category. A limitation of the TTC approach is that endocrine and developmental toxicity data are not incorporated. The Australia EPHC-NHMRC-NRMMC (2008) found that the TTC assessments by Kroes et al. (2004) provided insufficient protection when compared to traditional risk assessments. Their analysis found that the 95th percentile of uncertainty factors in traditional risk assessments was approximately 1500, and they therefore applied an additional safety factor of 15.

A subsequent analysis by the Minnesota Department of Health (MDH, 2017) examined the performance of TTC and LD_{50} values versus the RfDs for 614 non-carcinogens, culled from the same sources. The LD_{50} method was as or more protective than the RfD for 95% of the chemicals, while TTC was as or more protective for 83% of the chemicals. For cholinesterase inhibitors, the analysis showed that the LD_{50} and TTC methods were as or more protective than the RfD for 90% and 67%, respectively. Five of the seven chemicals with LD_{50}/RfD ratios > 10 were associated with developmental toxicity. For the 102 carcinogens in the panel, TTC was protective for 77% of the chemicals in comparison to the dose at the 10^{-5} (1 in 100,000) cancer risk level and for 90% at the 10^{-4} (1 in 10,000) risk level, while the LD_{50}-based approach was only protective for 40% of the carcinogens in the panel at the 10^{-5} risk level. FDA is in the process of revisiting the TTC methodology but is not expected to complete their review until 2020 (personal communication with Helen Goeden, MDH, April 1, 2019).

In another approach that can be used as a comparison, the Minnesota Department of Health (MDH, 2015) used toxicity factors (RfDs and cancer slope factors) from the USEPA Integrated Risk Information System (IRIS), the USEPA Human Health Benchmarks for Pesticides (HHBPs) and California EPA Public Health Goals to calculate 5th percentile Health-based Guidance (HBG) values for drinking water using RfDs for three categories of non-carcinogens, and 5th percentile 10^{-5} cancer risk values based on cancer slope factors and age-dependent adjustment factors. The non-carcinogenic HBGs were based on infant drinking water intake rate (0.289 L/kg-d) and a Relative Source Contribution factor of 0.5. The results are presented in the table below.

5th Percentile Health-based Guidance Values for Drinking Water Developed by Minnesota Dept. of Health (2015)

Category	n	RfD or Slope Factor	Drinking Water Guideline
Carcinogens	133	15 $(mg/kg/d)^{-1}$	0.006 µg/L (10^{-5} risk)
Non-carcinogens	666	0.1 µg/kg-d	0.2 µg/L
Cholinesterase inhibitors	46	0.035 µg/kg-d	0.05 µg/L
Endocrine-active compounds	99	0.017 µg/kg-d	0.3 µg/L

Despite this fascinating analysis, there is still the remaining difficulty of what to do with chemicals lacking even the basic data to assign them to the categories described above. Since many chemicals have been tested for LD_{50} and the LD_{50} approach is protective for the large majority of contaminants, at least for non-carcinogenic effects, this might be the most appropriate starting place.

For those chemicals that lack basic toxicological data, one can start with quantitative structure–activity relationship (QSAR) structural alerts via tools like Toxtree QSAR model (https://ec.europa.eu/jrc/en/scientific-tool/toxtree-tool), created and maintained by the Organization for Economic Development (OECD) of the European Commission. The OECD also has developed other related software (https://ec.europa.eu/jrc/en/eurl/ecvam/alternative-methods-toxicity-testing/computational-methods). Card et al. (2017) reported on the progress of the Estimation Prediction Interface (EPI) Suite, developed and maintained under the USEPA TSCA program by the Office of Pollution Prevention and Toxics. EPI Suite provides many different modules, covering not only molecular descriptors, quantum mechanical modeling and molecular dynamics modeling, but also metabolism and toxicokinetic disposition. The backbone of EPI Suite is the Distributed Structure-Searchable Toxicity (DSSTox) web application supporting data from 875,000 chemicals currently (USEPA, 2019) under the CompTox Chemistry Dashboard. The USEPA's National Center for Computational Toxicology is still working on a more advanced tool for generalized read-across (Helman et al., 2018, 2019) for the Dashboard. There is also a European Union Chemical Association (ECHA) read-across assessment framework (https://echa.europa.eu/documents/10162/13628/raaf_en.pdf) created under the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) program. The histories are summarized by Shah et al. (2016) and Williams et al. (2017). It is not

clear how much confidential business information that is needed for use in risk assessment of this sort databases will be available to state governments.

While the Dashboard, Toxtree and other products may be able to identify a similar chemical with sufficient toxicological data, one might also be able to combine the QSAR search with a TTC. As an example, one could look for a chemical structure alert for carcinogenicity and apply the TTC level for cancer to it. The TTC level could be set to the level approximating the 10^{-6} cancer risk level (that is used by New Jersey) among the comparison chemicals.

Limitations of the EPI Suite include exclusion of several types of chemical families for reasons including persistence and bioaccumulation, such as PFAS (Card et al., 2017). In addition, there are other important toxicity endpoints such as fetal toxicity that are not addressed.

An important question with implementing these approaches with systems that have two or more identified chemicals is how to consider the risks of multiple chemicals. To the extent that common points of action and mechanisms or type of tissue (such as those chemicals with hepatotoxic activity) can be identified, a risk assessor can use an approach based on adding fractions of the screening values such that the total does not exceed 1, analogous to a Hazard Index for RfDs.

MDH Approach for Pharmaceuticals

For pharmaceuticals the issue is how to assess the level of concern for a disparate group of chemicals and whether to conduct full, formal risk assessments or use methods that provide relatively quick recommendations for that group. In general, the pharmaceutical risk assessment universe has evolved differently from the environmental and occupational risk setting. There is only limited traditional toxicological guidance for drugs, in the form of Acceptable Daily Intake (ADI), which is analogous to the reference dose (RfD). The FDA and the FAO develop ADIs, but mostly for food contaminants such as pesticides and veterinary medicines, but there is some crossover between veterinary and human medicines.

There are various sources of information that can be used to develop ADIs for pharmaceuticals in addition to the usual sources like the National Library of Medicine. Among them are the FDA, the Drug Bank, the European Chemicals Agency (ECHA), and the Merck Index (Appendix).

For screening values of pharmaceuticals, some regulatory agencies (summarized in WHO, 2012) have begun to use the lowest (or minimum) therapeutic dose (LTD, mg/kg/day) modified by uncertainty factors (UFs) in a manner analogous to determination of an RfD. The UFs include those accounting for 1) human variability, 2) acute or subchronic dosage representing the LTD context in comparison to chronic exposure to drinking water contaminants, and 3) the fact that the LTD is analogous to a LOAEL. Adjustment factors (AFs) were also included for endocrine disruption and carcinogenicity. A UF can also be included for inadequacy of the toxicity database.

The Minnesota Department of Health (MDH) has developed the most extensive set of health-based screening values (Rapid Assessments for Pharmaceuticals: https://www.health.state.mn.us/communities/environment/risk/guidance/dwec/pharmproj.html), based on a decision tree (Suchomel et al., 2019). These include screening-Reference Doses and water screening values (WSVs). The former is calculated using an LTD (determined from several sources) divided by the cumulative uncertainty and adjustment factors (UFs and AFs). Analogous to the USEPA Lifetime Drinking Water Health Advisory (µg/L), the WSV includes a relative source contribution factor (RSC), typically 0.8 by default, and is divided by the drinking water intake for infants (0.289 L/kg/d). Other age-based values for water intake and exposure duration can be used, and lower RSCs can be inserted for commonly used over-the-counter medications such as acetaminophen and ibuprofen.

MDH published screening values for 119 active pharmaceutical ingredients (APIs) including metformin, metoprolol, sulfamethoxazole, valsartan and 3 opioids, but not carbamazepine, clofibrate and phenytoin. These 119 compounds represent the medicines considered relevant to drinking water contamination out of the 200 most frequently used medicines in Minnesota. Those identified as genotoxic or non-threshold carcinogens were not included, nor were non-oral agents or nutritional supplements.

Suchomel et al. (2019) noted that "UFs and AFs were applied with the following frequency:

- The Cancer AF (AF1) of 10 was applied to 9/119 (8 percent) of APIs.
- The Intraspecies UF (UF1) was applied to 119/119 (100 percent) of APIs.
- The LOAEL-NOAEL UF (UF2) of 10 was applied to 102/119 (86 percent) and the LOAEL-NOAEL UF (UF2) of 3 was applied to 17/119 (14 percent) of APIs.
- The Database UF (UF3) of 10 was applied to 2/119 (2 percent) and the Database UF (UF3) of 3 was applied to 101/119 (85 percent) of APIs.
- The Duration AF (AF2) of 10 was applied to 42/119 (35 percent) and the Duration AF (AF2) of 3 was applied to 50/119 (42 percent) of APIs.
- The Endocrine Activity AF (AF3) of 10 was applied to 41/119 (34 percent) and the Endocrine Activity AF (AF3) of 3 was applied to 4/119 (3 percent) of APIs.
- The overall Cancer or Endocrine Activity AF of 10 was applied to 46/119 (39 percent), and the overall Cancer or Endocrine Activity AF of 3 was applied to 4/119 (3 percent), according to the recommendations for calculating the overall UF for deriving the screening reference dose"

In addition, 10 LTDs were calculated on an age-adjusted body weight basis for children in the 6 to 17-year old range, and 3 LTDs were calculated for children based on dosing information for the medicine.

The methodology resulted in overall UFs/AFs ranging from 100 to 30,000. Of the 119 compounds, 33 (28%) had overall UFs/AFs >3000, and most of these had endocrine activity or had a LOAEL-NOAEL UF of 10. It should be noted that USEPA recommends that the total UF used in deriving a RfD not exceed 3000, a policy followed by MDH when performing full reviews.

Five of the calculated WSVs were compared to published corresponding in-depth health-based guidance values developed by MDH from laboratory animal or human data. All WSVs were at or below the traditional guidance values. The in-depth RfD-based values were higher than WSVs by factors of:

- 4 -22-fold for acetaminophen,
- 44-fold for carbamazepine,
- 2-fold for 17α-ethinyl estradiol,
- 250-fold for sulfamethoxazole, and
- 33-fold for venlaxafine.

The conclusion that WSVs would not be expected to exceed corresponding health-based guidance is reassuring, although it will undoubtedly be revisited. However, some of the WSVs are 1-2 orders of magnitude below the RfDs derived with the conventional approach, suggesting that they are unnecessarily stringent due to overuse of UFs and AFs.

Only two of the 119 pharmaceuticals were found in Minnesota surface waters at levels above the WSV, hydrochlorothiazide and methylprednisolone (Suchomel et al., 2018). None of the pharmaceuticals found in the Delaware River at the New Jersey American Water-Delran intake (the drinking water intake on the Delaware River that is furthest downstream) occurred at levels above the corresponding WSV developed by MDH (DRBC, 2017). Thus, pharmaceuticals may not be a priority focus of next steps in New Jersey.

Regarding persistence, the great majority of pharmaceuticals are metabolized and cleared from the body by design. However, there may be ecological persistence.

The MDH states that "screening values [for pharmaceuticals] are not designed or intended to be used to provide definitive estimates of risk" and suggested the following about use of the decision tree and screening values:

> • To set priorities for the derivation of new health-based guidance values. In situations where water screening values are particularly low and/or water detection values exceed the water screening value, MDH may choose to develop risk assessment guidance for the API [active pharmaceutical ingredients] using additional data and more refined risk assessment techniques.
>
> • To set priorities for new or improved laboratory analytical methods. In situations where water screening values for an API are particularly low and there are no detection data available for comparison, MDH may recommend that an analytical method be developed.

The water screening values provide a target for improved detection limits for specific APIs if the values are lower than established limits of current analytical techniques.

• To select APIs for future monitoring efforts. In cases where water screening values are particularly low and an analytical method exists for the API, MDH may recommend that the API be included in future monitoring studies to assess its risk in selected water sources.

• To assist in evaluating water quality. Comparing the monitoring results of water sources to the water screening values can provide an indication of whether the measured environmental level is unlikely to pose a health concern or warrant additional investigation.

Recommendations on the Use of Predictive Toxicity Approaches in Providing Guidance on CECs

The guidance provided by MDH for pharmaceuticals is also applicable to the use of screening level approaches and other predictive methods (e.g. *in vitro* data; read-across) discussed above for characterizing the toxicity of CECs.

In summary, it is reasonable to consider the predictions of toxicity and health risks from these approaches when:

- **Providing consumption advice to public water systems and private well users in situations of immediate concern**
- **Providing treatment advice to community water systems**
- **Setting priorities for**
    - **Research to provide needed toxicology data**
    - **Development of new or improved analytical methods**
    - **Monitoring of selected water sources**

However, approaches such as screening levels, *in vitro* toxicology data, and other predictive toxicology evaluations (e.g. read across) cannot be used as the basis for quantitative risk assessment for regulatory purposes at this time.

Citations

EPHC-NHMRC-NRMMC (2008). Australian Guidelines for Water Recycling. Augmentation of Drinking Water Supplies. Environmental Protection and Heritage Council, National Health and Medical Research Council, and National Resource Management Ministerial Council. Canberra, Australia.

Card ML, Gomez-Alvarez V, Lee W-H, Lynch DG, et al. (2017). History of EPI Suite and future perspectives on chemical property estimation in US Toxic Substances Control Act new chemical risk assessments. Environ Sci Processes Impacts, 19:203-213.

Clark C and Goeden H. (2017). Providing risk context for environmental contaminants with minimal toxicity data. Poster. Society for Toxicology Annual Meeting.

Cramer GM, Ford RA, and Hall RL. (1978). Estimation of toxic hazard – A decision tree approach. Food Cosmetics Toxicol. 16:255-276.

DRBC (2017). Delaware River Basin Commission. Appendix E: 2017 Monitoring Survey of PPCP and Hormones in Surface Water to Contaminants of Emerging Concern in the Tidal Delaware River Pilot Monitoring Survey. Delaware River Basin Commission, Trenton, NJ.

Helman G, Shah I, and Patlewicz G. (2018). Extending the Generalized Read-Across approach (GenRA): A systematic analysis of the impact of physicochemical property information on read-across performance. Comp Toxicol. *8*, 34-50.

Helman G, Shah I, Williams AJ, Edward J, Dunne J and Patlewicz G. (2019). Generalized Read-Across (GenRA): A workflow implemented into the EPA CompTox Chemicals Dashboard. *Altex*, 36: 462-465.

Goeden H, Suchomel A, Gavelis N, Bertelsen L, and Heiger-Bemays, W. (2014). Alternative approaches for evaluating and providing risk context for water contaminants with minimal toxicity data. Poster. Society for Risk Analysis Annual Meeting.

Kramer HJ, van den Ham WA, Slob W, Pieters MN. (1996). Conversion factors estimating indicative chronic no-observed-adverse-effect levels from short-term toxicity data. Regul Toxicol Pharmacol. 23(3):249-55.

Kroes R, Renwick AG, Cheeseman M, Kleiner J, Mangelsdorf I, Piersma A, et al., European Branch of the International Life Sciences Institute. (2004). Structure-based thresholds of toxicological concern (TTC). Guidance for application to substances present at low levels in the diet. Food Chem Toxicol, 42:65-83.

Minnesota Department of Health (2015). Executive Summary: Evaluating, Testing, and Reporting of Alternative Risk Assessment Methods (ARAM) Phase II: Risk Assessment Decision Framework.

Munro IC, Ford RA, Kennepohl E, Sprenger JG (1996). Correlation of structural class with no-observed effect levels: a proposal for establishing a threshold of concern. Food and Chemical Toxicology 34: 829–867.

Shah I, Liu J, Judson RS, Thomas RS, Patlewicz G. (2016). Systematically evaluating read-across prediction and performance using a local validity approach characterized by chemical structure and bioactivity information. Regul Toxicol Pharmacol. 79:12-24.

Suchomel A, Goeden H, Dady J. (2018). A Method for Developing Rapid Screening Values for Active Pharmaceutical Ingredients (APIs) in Water and Results of Initial Application for 119 APIs. Int J Environ Res Public Health 15(7) pii: E1308.

USEPA (2019). Dashboard. https://comptox.epa.gov/dashboard. Accessed July 16, 2019.

Williams AJ, Grulke CM, Edwards J, McEachran AD, Mansouri K, Baker NC, Patlewicz G, Shah I, Wambaugh JF, Judson RS, Richard AM (2017). The CompTox Chemistry Dashboard: a community data resource for environmental chemistry. J Cheminform. 9(1):61.

WHO (2012). Pharmaceuticals in Drinking-Water. Geneva, Switzerland.

Appendix B. NJDEP SAB CEC Committee Analytical Methods Workgroup

Our ability to detect and identify unknowns continues to improve dramatically with the introduction of more reasonably priced high-resolution mass spectrometric instrumentation. The approach using molecular formula, derived from an accurate mass, has seen proposed standardization in reporting confidence in the identification of the unknown compounds (Schymanski et al., 2014). Tentative identification of an unknown is supported by mass fragments, library searching of ever-expanding commercial libraries and commercial software that uses accurate mass for structure prediction. The highest degree of confidence is still thought to be confirmatory analysis with a commercial standard on the same instrument with the same operating conditions. High correlation to a literature-reported spectral scan of the TIC is just short of this degree of confidence. While library matches are still more difficult for LC/MS unknowns, this landscape is also changing. The problem of significantly different spectra being created by a differences in operating conditions or, perhaps more dramatically, a difference in instrument platforms is becoming less of a factor when making comparisons to literature-reported mass spectra.

However, USEPA methods have not kept pace with these innovations. While USEPA does have performance-based methods that allow instrument operators to maximize the utility of their measurement methods, these methods are not recognized for some compliance testing requirements, although fortunately most discovery studies of unknowns do not fall under a need for compliance. Performance-based methods are those that do not specify an analyte but rather allow the operator to optimize the operating conditions of the instrument for whatever analyte the operator chooses. More specifically, performance-based method, unlike most of the other USEPA analysis methods, do not specify the type of instrument (e.g. HPLC single quadrupole), but rather describe an ability to measure, specifying the performance the method must achieve. A performance-based method would allow the flexibility for substitution of any LC/MS method (e.g. UPLC/QQQ or HPLC/ToF) to quantify a contaminant class as long as it can achieve the required metrics (e.g. Practical Quantitation Level [PQL], limit of detection [LOD], repeatability). Acceptance of performance-based methods will allow laboratories and regulatory agencies to better keep up with the next contaminant that is the focus of current attention. Performance-based methods can be used for recently identified contaminants before a new compound specific method is proposed and adopted in the Federal Register. They allow for more flexibility and offer more promise for hitting, or coming close to, a moving target (new contaminant) of public interest. They can be used to develop methods that screen for hundreds of compounds in a single assay across multiple compound classes.

USEPA has begun to recognize the need to identification of unknowns and broad-based screening methods when measuring contaminants. The have begun by using a round robin of 30 labs and a reference standard from 1200 chemical substances in their ToxCast library, through

their ENTACT program (Sobus et. al, 2018) See: https://www.epa.gov/sciencematters/epas-entact-study-breaks-new-ground-non-targeted-research.

There is also the CompTox Chemical Dashboard, an interactive database developed by USEPA: "*Chemical features observed using high-resolution mass spectrometry can be tentatively identified using online chemical reference databases by searching molecular formulae and monoisotopic masses and then rank-ordering of the hits using appropriate relevance criteria*". See: https://cfpub.epa.gov/si/si_public_record_report.cfm?Lab=NCCT&direntryid=334220

Both ENTACT and the CompTox database will provide formats for unknown identification and, when coupled with performance based analytical methods, should allow for much more flexibility in measuring new contaminants. This could enable the implementation of guidelines and possibly standards for such new contaminants before compound-specific analytical methods can be developed.

The focus of the SAB CEC Workgroup is on drinking water. However, high use industrial production water or waste streams from sources of contamination are also important and should be considered when discussing emerging contaminants. Water used in industrial processes should be treated prior to discharge into the environment and should be of a similar quality as the water that entered the facility. When analytical methods are required to validate a compound's removal, drinking water methods should be more than sensitive enough to meet this requirement. However, when investigating emerging contaminants in wastewater, it must be recognized that wastewater is a much more complex matrix than drinking water. Therefore, the methods used for wastewater are not identical to those used for drinking water, and the detection and reporting levels may be higher for wastewater than for drinking water. Analytical methods for wastewater should be recognized as necessary and addressed from the standpoint of applying matrix compensation techniques to drinking water methods.

Exotic instrumentation needed for the analysis of many of the compounds of emerging concern will likely never be routinely used by a large number of water utility laboratories. Most water systems do not have their own laboratory. Currently, the best-equipped water utilities have labs with the sophisticated and expensive instrumentation required for these types of analyses. Smaller commercial laboratories add methods only as regulations require and larger laboratories that can do the analysis often charge higher price for unregulated contaminants because the analysis is not requested as often. Most public water systems will outsource laboratory analyses, especially for emerging contaminants, to a few high-powered commercial laboratories.

As discussed in more detail above, New Jersey regulatory limits are set at the health-based goal if achievable based on analytical considerations. They are set above the health-based goal, based on analytical and treatment considerations, if necessary. For a regulatory agency to promulgate drinking water regulations with specific monitoring requirements, certain realities must be

considered. There is a question about whether enough certified laboratory capacity will be immediately available for any emergent contaminant at the analytical sensitivity required. For some contaminants, health-based goals will fall well below the level that can be reliably measured by conventional instrumentation capabilities (i.e. the Practical Quantitation Level; PQL). When this occurs, the enforceable standard is set at the PQL. For such contaminants, the compound is regulated based on analytical limitations, rather than the health-based goal, often creating a compromise that stands for many years after the regulation is adopted. For example, the New Jersey Drinking Water Quality Institute's 2009 review of the basis for existing New Jersey drinking water standards (DWQI, 2009) concluded that the Practical Quantitation Levels for many contaminants should be decreased to reflect improvements in analytical capabilities, including several contaminants for which the drinking water standard is set at the PQL rather than the lower health-based value.

A second limitation to the analytical response to regulations about emerging contaminants is that most commercial laboratories use only methods published in the Code of Federal Regulations (CFR). While many research-driven investigators pursue emerging contaminants with rigor, it is usually within the confines of their own objectives and few take the time to convert a published method to one adopted by agencies such as the USEPA. Performance-based methods, not tied to either a specific contaminant or even a specific class of contaminants, provide the best opportunity to quantify an emerging contaminant in a timely fashion, without waiting for an analytical method to be published in the CFR.

A third limitation in matching the analytical capability to a recently adopted regulation on an emerging contaminant is the cost and availability of the instrumentation. Even with availability of performance-based methods or other new methods to analyze an emerging contaminant, the number of laboratories who would be prepared to run the method with the desired reliability would be very limited. The cost for many if not all of these assays would be considered custom, until the actual conditions could be verified. Most water purveyors must use a commercial laboratory for these methods as they cannot afford the cost of either the instrumentation or the personnel to run the sophisticated instruments (HPLC/ MS/MS) to perform the assay. It is therefore recommended that adequate lead time be provided when regulations requiring new or updated analytical methods are adopted to allow for development of sufficient commercial laboratory capacity

Availability of commercial standards presents other challenges. While there is a desire to maximize efficiency with a given laboratory analysis, the use of surrogates or indicators is not without difficulties. An example might be analytical methods for Total PFAS. Efforts to identify every PFAS present in a water sample would likely be unproductive. It is generally acknowledged that specific analytical methods underestimate (and probably significantly underestimate) the total concentration of PFAS. Quantitative analysis requires the use of calibration standards, which simply do not exist for most PFAS. Approaches such as the Total

Oxidizable Precursor (TOP) assay or the Extractable Organic Fluorine (EOF) have been developed to provide estimates of total PFAA precursors and total PFAS, respectively (McDonough et al., 2019). Often when standards are not available for individual analytes, a total "class" measurement is reported. There is a need to exercise caution when extrapolating data and potential toxicity from such "total" measurements, as discussed in the PFAS Case Study (Appendix D). Data users must be cautious when inferring equivalent adverse health effects among all of the compounds comprising the "total" analysis. While these limitations are generally well known among those running the tests, other data users may not be as cautious in their interpretation of the measurements. While PFAS is provided as an example above, it should be noted that each class of compounds has unique analytical considerations and must be evaluated individually.

- Limitations of conclusions based on analytical methods that estimate "totals" for a class of compounds include assumptions that all compounds in the class:
    - have a similar measurement response for each compound (semi-quantitative).
    - have equivalent chemical/physical properties.
    - have similar toxicological properties (a read-across approach).

- The CEC SAB is aware that NJDEP and the NJ Drinking Water Quality Institute have established a process for development of drinking water, groundwater, and soil standards in which the health-based level is used to guide the selection of analytical methods with appropriate sensitivity. The regulatory standard cannot be set below the level that can be reliably measured (i.e. the PQL), and the goal is that the analytical method will have a PQL below the health-based level. If the PQL must be set above the health-based level, it is set as close to the health-based level as possible. Similarly, for unregulated contaminants of emerging concern, Health Reference Levels or some indicator of a concentration of relevant adverse health effects should assist in the selection of analytical methods or in the grouping of emerging contaminants.

There is still a great deal of discussion without consensus about grouping contaminants as classes, and basing such groupings on chemical and physical properties is only a start. While it may be tempting to classify chemicals broadly, differences in toxicology or laboratory method can quickly complicate the situation.

Citations:

DWQI (2009). New Jersey Drinking Water Quality Institute. Hazardous Contaminants. https://www.state.nj.us/dep/watersupply/g_boards_dwqi_haz.html

McDonough, CA, Guelfo, JL, Higgins, CP. 2019. Measuring total PFASs in water: The tradeoff between selectivity and inclusivity. Current Opinion in Environmental Science & Health 7: 13-18.

Schymanski, E.L., Jeon, J., Gulde, R., Fenner, K., Ruff, M., Singer, H.P. and Hollender, J., 2014. Identifying small molecules via high resolution mass spectrometry: communicating confidence. *Environ. Sci. Technol.* 2014, 48, 4, 2097-2098

Sobus, J.R., Wambaugh, J.F., Isaacs, K.K., Williams, A.J., McEachran, A.D., Richard, A.M., Grulke, C.M., Ulrich, E.M., Rager, J.E., Strynar, M.J. and Newton, S.R., 2018. Integrating tools for non-targeted analysis research and chemical safety evaluations at the US EPA. *Journal of exposure science & environmental epidemiology*, *28*(5), pp.411-426

Appendix C. NJDEP SAB CEC Committee Treatment Technologies Workgroup

WASTEWATER TREATMENT TECHNOLOGIES AND CEC REMOVAL

Described below are different treatment technologies as they relate to different broad classes of compounds for comparison across different groups. The methods described below are those methods either currently in place or may be added if specific water sources have high levels of specific classes. Within the main text is a summary table with the relative effectiveness for each broad group of compounds as well as specific treatment approaches. If a specific compound or group within a class are selected to be reference compounds

Grit Removal and Primary Clarification:

Primary treatment is ineffective in removal of most contaminants of emerging concern with removal mainly by sorption to primary sludge. Some **personal care products** have been found to have moderate removal through primary treatment (fragrances 40%). **Pharmaceuticals** have moderate to low removals (0% - 28%) dependent on contaminant characteristics.

Secondary Biological Treatment:

CEC removal in biological treatment is driven by the chemical properties of the CEC and can be removed through adsorption, volatilization and biotransformation. Hydrophobic contaminants will likely be adsorbed to suspended solids, extracellular polymeric substances, and/or microbial cell membranes in activated sludge. Positively charged contaminants will likely be adsorbed to the mainly negatively charged surfaces in activated sludge. Volatile compounds can be removed through transfer of contaminants from water to air, depending on Henry's law constant, temperature, and pressure. Finally, hydrophilic organic contaminants are mainly removed through biotransformation, however, this is dependent on metabolic and co-metabolic function of the microbial community and process parameters like hydraulic retention time and solid retention time.

Surfactants: Relatively high removal for most household surfactants (>95%).

Pharmaceuticals: Removal very dependent on contaminant characteristics (0-100%), most contaminants are hydrophilic and negatively charges making biotransformation the main removal mechanism.

Illicit drugs: Relatively high removal with the exception of MDMA (79% - >98%, MDMA 0-26%).

Personal Care Products: Removal dependent on contaminant characteristics. Fragrances tend to be hydrophobic and are removed by adsorption (60% - 99%). Antimicrobials (Chloroxylenol, Triclosan and Triclocarbon) often well removed by

activated sludge (>80% or 55% - 99%). Insect repellents (DEET) removal is highly variable (10% - 99%) depending on plant and season. UV filtering sunscreens are very well removed due to biodegradability and adsorption (>90%).

Household Chemicals: Removal dependent on contaminant characteristics. Food additive removal in activated sludge varies widely (5% - 99%). Chelating agents removal is also highly variable (90% - 97% for NTA, <10% for EDTA).

Plasticizers: Partial to high removal for most plasticizers through sorption and biodegradation (60% - 90%).

Flame Retardants: Highly variable removal based on contaminant characteristics (<5% - >90%).

Perfluorinated Compounds: Very low removal in activated sludge (<5%).

Pesticides: Typically low removal (<50%).

Synthetic Organic Compounds: Dependent on contaminant characteristics. Many are hydrophobic and have low biodegradability and therefore are mainly removed through sorption (75%).

Inorganics: Associate with suspended solids and therefore are partially to well removed (>75%, Nickle only 30%).

Filtration

Removal of contaminants in filtration is driven by their association with solids in wastewater. Therefore, certain **pharmaceuticals**, **inorganics** (metals), hydrophobic **pesticides**, some **flame retardants**, some **plasticizers** (phthalates), certain **household chemicals** (UV filtering sunscreens, triclosan, fragrances) will be removed via filtration. However, several **pharmaceuticals** were reported to have low removal (<44%), as well as **fire retardants** (TCEP 0%) and **pesticides** (0% - 14%).

Conventional Disinfection (UV and Chlorine)

UV: UV alone can only remove certain compounds based on their characteristics with **pharmaceutical** removals varying greatly (<20% - >80%), high removal of some **personal care products** (Triclosan 50% - >80%), and low removal of some **fire retardants** (TCEP <20%).

Chlorine: Highly variable removal based on contaminant characteristics. **Pharmaceutical** removal highly variable (0% - 62%). **Pesticides** have low removal (Atrazine and DEET 0%). And **plasticizers** and **fire retardants** also have low removal (BPA 11% and TCEP 0% respectively).

Advanced Oxidation Processes

Mainly Ozonation and UV/H_2O_2 are used to form hydroxyl radicals (•OH) which in turn oxidize certain contaminants based on contaminant characteristics.

Ozone: Ozone has been shown to degrade **personal care products** (UV filters, fragrances, antimicrobials >79% at 15 mg/L ozone) and several **pharmaceuticals** (carbamazepine, diclofenac, indomethacin, sulpiride and trimethoprim >95% at 5 mg/L ozone). And low removal of **fire retardants** (TCEP 0% - 10%).

UV/H_2O_2: Much higher rate of degradation compared to just UV treatment alone. High removal of select **pharmaceuticals** with variation dependent on dose (50% - 100%). High removal of **personal care products** (Triclosan >80%) and **pesticides** (Atrazine 100%). And low removal of **fire retardants** (TCEP <20%).

Activated Carbon

Powdered activated carbon (PAC): PAC addition has been shown to improve contaminant removal through sorption of contaminants. Dependent on PAC dose, contaminant characteristics (K_{OW}), and wastewater composition (DOC). Removal of **pharmaceuticals** is mostly high (Diclofenac, Carbamazepine, Propranolol >90%, Sulfamethoxazole 2% - 62%).

Granular activated carbon (GAC): Also improves contaminate removal depending on dose, contaminant characteristics, and wastewater composition. **Pharmaceutical** removal highly variable (17% - 100%) depending on contaminant and adsorption capacity of GAC. Low removal of **pesticides** (DEET 15%) and variable removal of **personal care products** (triclosan 0% - 95%) have been reported.

APPENDIX D: CASE STUDY: CAN PFAS BE GROUPED AND ADDRESSED BASED ON COMMON TOXICITY AND/OR REMOVAL BY THE SAME TREATMENT TECHNOLOGY?

Introduction

Per- and polyfluoroalkyl substances include thousands of chemicals (OECD), and mixtures of PFAS are often found in the environment, including in drinking water. Their presence in the environment arises from their use in industrial processes and commercial/consumer products, their formation as unintended byproducts of manufacturing processes (McCord and Strynar, 2019), and their presence as complex mixtures in aqueous film forming foams used in firefighting and training.

Toxicological information relevant to development of drinking water guidance is available for only relatively few PFAS, primarily perfluoroalkyl acids (i.e. perfluoroalkyl carboxylates and perfluoroalkyl sulfonates). The PFAS that have been studied in laboratory animals often caused the same general types of toxicological effects, including hepatic, developmental, reproductive, immune system, thyroid, and/or neurobehavioral. . Several PFAS (PFOA, PFOS, GenX) caused tumors in rats, while PFHxA did not. However, the specific endpoints of toxicity, doses at which effects occur, and modes of action vary among PFAS. Only a few studies have evaluated toxicological interactions of two or more PFAS.

When considering approaches for addressing PFAS in drinking water as a group, it must be emphasized that the identity and concentrations of PFAS known to be present is dependent on the analytical method and the Reporting Levels that were used (McDonough et al., 2019). For a toxicological evaluation of a mixture of PFAS, information on the specific PFAS that are present is needed - and an estimate of total PFAS concentration is not sufficient. This is also the case for toxicity evaluations of mixtures of PCBs for which congener-specific analysis, rather than total Aroclor concentrations, is needed. USEPA Method 537.1, currently used for routine drinking water analysis, can include up to 18 PFAS – 12 perfluoroalkyl acids (9 carboxylates, 3 sulfonates), 2 PFOS precursors, and 4 replacements (GenX, ADONA, and two isomers of F53-B). Non-target analysis using high resolution mass spectrometry, currently used primarily for research, may tentatively or positively identify numerous additional PFAS, even in the absence of analytical standards. Other methods such as the Total Oxidizable Precursor (TOP) assay or the Extractable Organic Fluorine (EOF) provide estimates of total PFAA precursors or total PFAS, respectively, without identification of individual compounds. This information cannot be used as the basis for a toxicological evaluation, but it can potentially be used to evaluate the effectiveness of treatment removal technologies for PFAS, based on the decrease in total precursors or total PFAS after treatment.

Potential approaches for consideration of PFAS in drinking water as a group

Chemical-by-chemical approach

The current New Jersey Health-based MCLs for three long-chain PFAS (PFOA, PFOS, PFNA) were developed using the traditional chemical-specific risk assessment approach involving detailed evaluations of relevant human, animal, and mode of action data. Drinking water guidelines for individual long-chain (PFOA, PFNA, PFOS, and/or PFHxS) and short-chain (PFBA, PFBS, PFHxA, and/or GenX) by several other states (CA, MI, MN, NH, NY) were developed with a process that is similar, although generally not as thorough, as New Jersey's.

The advantage of this approach is that the drinking water guidelines are based on chemical-specific information. Specifically, they are based on the most sensitive known toxicological endpoints that are considered adverse, well established and relevant to humans based on mode of action analysis, and they also consider chemical-specific differences in animal and human toxicokinetics.

This chemical-specific approach does not take into account the potential for toxicological interactions toxicity when multiple PFAS, including those which may not have been detected, co-occur. However, as stated in the DWQI MCL recommendation documents, drinking water treatment (most commonly GAC) used to remove regulated long-chain PFAAs will also remove other PFAS, both identified and unknown, to a greater or lesser extent. Relevant to this point, longer-chain PFAS (including both PFAAs and other types of PFAS such as per- and polyfluoroethers) are of greater human health concern than shorter chain PFAS due to their propensity for human bioaccumulation (NC State University, 2018). These longer chain PFAS, regardless of their structure, are also likely to be more efficiently removed by GAC treatment than shorter chain PFAS.

The chemical-specific approach is very resource intensive, and only a limited number of contaminants can be addressed in this way by the DWQI and/or NJDEP. It is unclear whether the frequency and levels of additional long-chain PFAAs (e.g. PFHxS) in NJ public water systems, in the absence of co-occurrence of regulated/soon to be regulated PFAS (PFOA, PFOS, PFNA), is sufficient to warrant a chemical-specific risk assessment. A possible approach to address such occurrences might be to use a guideline developed by another state, after thorough review, as a NJ guidance value. Importantly, there is insufficient information to develop traditional chemical-specific risk assessments for certain other PFAAs (e.g. PFHpA, C7) that are detected with standard analytical methods, while noting that it is similarly unclear whether these other PFAS occur at levels of potential concern in NJ drinking water, in the absence of PFOA, PFOS, or PFNA.

For PFAS other than PFAAs (with the exception of GenX and possibly a few others), there are generally little or no publicly available toxicity data. It is therefore unlikely that the data needed

for a traditional chemical-specific risk assessment will be available for most other unregulated PFAS that may be identified in NJ drinking water with non-target analysis or other non-standard analytical methods. However, as discussed for unregulated contaminants in general in the main section of this report, a precautionary approach should be used for those PFAS that have any data indicating low-dose toxicity and/or potential for human bioaccumulation.

Short-chain PFAS have much shorter half-lives than long-chain PFAS. Therefore, same external dose results in a much lower internal dose (e.g. blood serum level) for short-chain PFAS. For this reason, long-chain PFAS generally cause toxicity at much lower doses than short-chain PFAS, and drinking water guidelines for short-chain PFAAs developed by other states are generally several orders of magnitude (typically 100s to 1000s of ng/L) than for long-chain PFAS (<10 – 50 ng/L). Based on currently available occurrence data and other states' drinking water guidelines, it appears to be unlikely that these short-chain PFAAs (PFBA, PFBS, PFHxA) will be found frequently at levels of concern in New Jersey drinking water.

Consideration of total concentration of long-chain PFAS in drinking water

In contrast to the chemical-by-chemical approach described above, several states (VT, MA, CT) use (or plan to use) a drinking water guideline based on the total concentration of 5 or 6 long chain PFAS (PFHpA – C7; PFOA, PFNA, PFDA – C10 [MA only], PFHxS, and PFOS). The total concentration of long-chain PFAS is based on the chemical-specific value for PFOA and PFOS, which happens to be the same for both compounds (e.g. 20 ng/L in VT and MA; 70 ng/L in CT). Similarly, the USEPA Health Advisory for PFOA and PFOS is based on the total concentration of both PFAS not exceeding the individual Health Advisory for each compound of 70 ng/L. These approaches assume that the toxic effects, potencies, and human half-lives of the long chain PFAS that are combined are similar enough to be considered the same , and that their toxicity can be assumed to be additive.

This approach is more stringent than guidelines for the individual PFAS and requires assumptions in the absence of scientific data. For example, although there is virtually no toxicity information for PFHpA (C7) and available data indicates that it is excreted more rapidly than PFOA, this approach uses the health protective assumption that the human health risk of C7 is equal to longer chain PFAS including PFOA, PFOS, and PFNA.

A more general issue is that the toxicological potencies, most sensitive toxicological endpoints, and modes of action clearly are not the same for all of the long-chain PFAS included in these groupings. This is illustrated by the results of the 28 day rat studies (NTP, 2019a; NTP, 2019b) that included all of the long-chain PFAS mentioned above (except PFHpA). In these studies, the relative potencies of these PFAS differed for different effects (hepatic and thyroid), and also between males and females for the same effect and compound in some cases.

Furthermore, the most sensitive endpoints of toxicity differ among these long-chain PFAS. For example, literature reviews by the DWQI and others indicate that immune system suppression is a very sensitive toxicological endpoint for PFOS, while hepatic effects appear to be more sensitive than immune effects for PFOA.

Finally, evaluations by the DWQI and others indicate that the mode(s) of action for toxicity also differs among these long-chain PFAS. For example, PPAR-alpha activation is partially responsible for the hepatic and developmental effects of PFOA, while these same effects appear to be totally or primarily PPAR-alpha independent for PFOS.

Based on the considerations discussed above, it is concluded that application of this approach to long-chain PFAS is a precautionary decision that is protective of public health, but it is not totally supported by scientific considerations. The larger class of all PFAS beyond long-chain PFAAs includes compounds with diverse structures, physical-chemical properties, human half-lives, and target endpoints. Based on the assumptions needed to apply this approach to a the more closely related PFAS subgroup of long-chain PFAAs, an approach based on the even more uncertain assumptions needed for estimation of toxicity based on the total concentration of all detected PFAS is not recommended.

Relative Potency Factor approach

This approach is based on applying Relative Potency Factors (RPFs) for a common toxicological effect to estimate the toxicity of a PFAS mixture. It is similar in concept to the Toxicity Equivalency Factors [TEFs] used for acetylcholinesterase inhibitors and for dioxins, furans and dioxin-like PCBs.

The Netherlands Institute for Public Health (RIVM, 2018) has developed a Relative Potency Factor (RPF) approach for 18 PFAAs, including 13 carboxylates (C4-C18) and 5 sulfonates (C4, C5, C6, C7, C8, and C10). The RPFs are based on comparison of the lower confidence limits on the benchmark dose (BMDLs) for a 5% increase in relative liver weight in male rats after exposures ranging from 6 to 13 weeks. PFOA was used as the index compound with an RPF of 1, and the RPFs for other PFAS ranged from 0.001 for PFBS to 10 for PFNA. The data needed to develop a BMDL and RPF were available for 11 of the PFAAs, and the RPFs for the other 7 PFAS were estimated by interpolation from chemicals with longer and shorter chain lengths. In this approach, the RPFs are applied to the concentration of each PFAS present in environmental media such as drinking water, and the total is compared to the RIVM Health-based Guidance Value for PFOA.

RIVM (2018) states that liver hypertrophy is the most sensitive toxic endpoint for PFOA and PFOS, and that this may progress to more severe forms of hepatic toxicity. They therefore concluded that hepatic effects should be used as the basis for comparison of relative potency among PFAS. However, as mentioned above, the most sensitive toxicological effect vary among

PFAS. While most or all PFAS that have been tested caused increased liver weight and hepatocyte hypertrophy, other effects are more sensitive for specific PFAS including delayed mammary gland development for PFOA (DWQI), immune system suppression for PFOS (DWQI and others), kidney toxicity for PFBS (MDH), and effects on thyroid hormones for PFHxS (MDH). These effects may not have been found to be more sensitive than liver hypertrophy for some other PFAS, and they have been not been evaluated for many other PFAS.

Additionally, as discussed in the main section of this report, the TEF approach for acetylcholinesterase inhibitors and for dioxins and related compounds assumes that toxicity occurs through the same mechanism of action or target receptor for all compounds in the class. RIVM (2018) discusses that the European Food Safety Authority (EFSA) also uses this approach to predict the toxicity of mixtures of pesticides that cause toxicity to the nervous system and thyroid system, regardless of whether or not a common mode of action is involved, and has proposed to do so for other organs/systems including the liver. However, it is less clear that hepatic toxicity of multiple compounds that occurs through differing modes of action can be assumed to be additive than when the modes of action are the same.

Additionally, the BMDLs and RPFs developed by RIVM (2018) are based on the external (administered) doses to the male rats. While the BMDLs for increased liver weight are impacted by the half-lives in male rats, the RPFs do not account for differences in the relative half-lives between humans and male rats (i.e. differences in the male human:male rat half-life ratio). Based on the half-lives presented in RIVM (2018), the human:male rat half-life ratios range between 8 for PFBA and ~500 for PFOA, and consideration of these differences would substantially affect some of the RPF values.

Because of the considerations discussed above, the RIVM (2018) approach based on Relative Potency Factors for a common endpoint (such as increased liver weight) is not recommended by the SAB. It should also be noted that this approach is only applicable to compounds for which the relative potency for the effect used for the RPFs is known (e.g. PFAAs, GenX, possibly a few other PFAS), or can be estimated from closely related compounds. Therefore, aside from the other considerations discussed above, this approach is not applicable to mixtures that include the large number of PFAS that lack known or estimated toxicity data for the target effect.

Predictive approaches for contaminants with limited data

The CEC SAB agrees with the conclusions of Card et al. (2017) that, because of their unique physical-chemical, toxicokinetic and toxicological properties, PFAS are not amenable to the current approaches for predicting toxicity for contaminants with limited data such as QSAR and related methods discussed in Appendix A.

Approach based on high-throughput testing

Many PFAS lack toxicological data, and it is not feasible to conduct *in vivo* studies for large numbers of PFAS. To address this issue, USEPA and NTP have undertaken a research program aimed at developing high throughput testing approaches that can rapidly predict the toxicity of PFAS that lack toxicological data. This effort includes *in vitro* assays that will provide toxicological and toxicokinetic data. The initial group of PFAS to be tested includes compounds with *in vivo* data that can be used to validate the *in vitro* assays and other compounds selected for their structural diversity, to "span the chemical space" of PFAS. It is hoped that toxicity for other PFAS, and mixtures of PFAS, to be tested in the future can be predicted from the results of the initial set of compounds (Patlewicz et al., 2019). These approaches are still being developed, and technical issues related to both the procedures used to conduct the assays and the interpretation of the results must be resolved before they can be used for routine toxicity screening. Additionally, current risk assessment guidelines do not provide for use of this type of information as the basis for drinking water guidelines or other risk assessments. As such, use of these data to develop such guidelines would require a change in risk assessment guidance.

Conclusions and Recommendations

PFAS are a large group of compounds with diverse structures, physical-chemical properties, human half-lives, and toxicological effects. The toxicity of PFAAs has been studied more thoroughly than for other types of PFAS, and publicly available toxicity data are available for only a few other PFAS. As it is not feasible to perform toxicity studies in laboratory animals for large numbers of PFAS, there is a need to evaluate potential approaches for more rapid toxicity evaluation of PFAS individually and as a group.

While only a few PFAS (PFOA, PFOS, PFNA) are or soon will be regulated in NJ, drinking water treatment (most commonly GAC) used to remove these regulated long-chain PFAAs will also remove other PFAS, both identified and unknown, to a greater or lesser extent. Relevant to this point, longer-chain PFAS (including both PFAAs and other types of PFAS such as per- and polyfluoroethers) are of greater human health concern than shorter chain PFAS due to their propensity for human bioaccumulation (NC State University, 2018). These longer chain PFAS, regardless of their structure, are also likely to be more efficiently removed by GAC treatment than shorter chain PFAS.

Potential approaches for addressing PFAS in drinking water as a group based on common toxicity were evaluated. These approaches include the total concentration of long-chain PFAAs based on a chemical-specific concentration for a well-characterized PFAA such as PFOA, and a Relative Potency Factor approach based on relative toxicity for a common toxicological effect such as increased liver weight The SAB concluded that these are precautionary approaches that are not totally supported by scientific data for even the limited groups of PFAAs for which they are being used, and that they are not applicable to a larger universe of many types of PFAS with different structures.

The SAB concluded that unregulated PFAS that are detected in NJ drinking water should not be ignored, especially when they have a considerable toxicological database. Traditional chemical-specific risk assessment for PFAS is resource intensive, and it is not feasible for NJ scientists to develop such assessments for large numbers of PFAS . For PFAAs that occur infrequently at levels of potential concern in NJ drinking water in the absence of co-occurrence with regulated PFAS, use of drinking water guidelines developed by other states as NJ guidance, after thorough review by NJDEP, could be considered.

It is unlikely that sufficient toxicity data to develop chemical-specific guidelines will be available for most PFAS of other types that may be found in NJ drinking water using non-standard analytical methods. However, a precautionary approach should be taken if the available data suggest low-dose toxicity or the potential for human bioaccumulation.

Current computational approaches used to predict toxicity for other types of contaminants that lack toxicity data may be useful for evaluation of PFAS, while recognizing that some of these approaches may not be applicable to PFAS due to their the unique physical-chemical and biological properties. High throughput testing programs that are currently underway at USEPA and NTP may provide a future approach for rapid evaluation of toxicity of individual PFAS and PFAS mixtures. It is recommended that NJDEP toxicologists remain aware of the progress of this effort and its applications in risk assessment.

Citations

Card ML, Gomez-Alvarez V, Lee W-H, Lynch DG, et al. (2017) History of EPI Suite and future perspectives on chemical property estimation in US Toxic Substances Control Act new chemical risk assessments. Environ Sci Processes Impacts, 19:203-213.

McCord, J, Strynar, M. 2019. Identification of Per- and Polyfluoroalkyl Substances in the Cape Fear River by High Resolution Mass Spectrometry and Nontargeted Screening. Environ Sci Technol. 53:4717-4727.

McDonough, CA, Guelfo, JL, Higgins, CP. 2019. Measuring total PFASs in water: The tradeoff between selectivity and inclusivity. Current Opinion in Environmental Science & Health 7: 13-18.

NC State University. 2018. GenX Exposure Study Blood Sample Results. https://genxstudy.ncsu.edu/files/2019/08/Wilmington-Nov-2018-blood-results.pdf

NTP (2019a). National Toxicology Program. Technical Report on the Toxicity Studies of Perfluoroalkyl Sulfonates (Perfluorobutane Sulfonic Acid, Perfluorohexane Sulfonate Potassium Salt, and Perfluorooctane Sulfonic Acid) Administered by Gavage to Sprague Dawley

Rats. NTP TOX 96. August 2019.
https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox096_508.pdf?utm_source=direct&utm_medium=prod&utm_campaign=ntpgolinks&utm_term=tox096

NTP (2019b). National Toxicology Program. Technical Report on the Toxicity Studies of Perfluoroalkyl Carboxylates (Perfluorohexanoic Acid, Perfluorooctanoic Acid, Perfluorononanoic Acid, and Perfluorodecanoic Acid) Administered by Gavage to Sprague Dawley Rats. NTP TOX 97. August 2019.
https://ntp.niehs.nih.gov/ntp/htdocs/st_rpts/tox097_508.pdf?utm_source=direct&utm_medium=prod&utm_campaign=ntpgolinks&utm_term=tox097

OECD. Organisation for Economic Co-operation and Development. Toward a New Comprehensive Global Database of Per- and Polyfluoroalkyl Substances (PFASs). Posted at:
https://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/

Patlewicz G, Richard AM, Williams AJ, Grulke CM, Sams R, Lambert J, Noyes PD, DeVito MJ, Hines RN, Strynar M, Guiseppi-Elie A, Thomas RS. A Chemical Category-Based Prioritization Approach for Selecting 75 Per- and Polyfluoroalkyl Substances (PFAS) for Tiered Toxicity and Toxicokinetic Testing. Environ Health Perspect. 127:14501. Open access at
https://search.proquest.com/openview/da45940e7a159238dd6931f2bb383d53/1?pq-origsite=gscholar&cbl=2026371

RIVM (2018). Netherlands National Institute for Public Health and the Environment. Mixture exposure to PFAS: A Relative Potency Factor approach.
https://www.rivm.nl/bibliotheek/rapporten/2018-0070.pdf

APPENDIX E: COMPARISON OF NJRISK AND USEPA CHEMISTRY DASHBOARD (prepared by Brian Pachkowski, NJDEP Division of Science and Research)

NOTE: This comparison is based on the versions available in September 2018 and does not reflect updates since that date.

	NJRisk	Chemistry Dashboard
Publicly available?	No; only accessible by NJDEP staff http://www.njrisk.org/wp-login.php	Yes https://comptox.epa.gov/dashboard
Background information	**METIS (chemical screening tool)** • retrieves and assembles information from over 1,400 publicly available databases • information may contain, but are not limited to, physical and chemical properties, hazard, toxicological, environmental and regulatory information **Risk Ranking (METIS + PRoTEGE)** Tier I: based on chemicals in USEPA's Chemical Data Reporting (CDR) database Tier II: case study of selected chemicals	• Accesses data from nine component databases (mostly USEPA- and NIH-based) • Information includes physical and chemical properties, hazard, toxicological, environmental and regulatory information
Number of chemicals that can be searched	Varies; depending on search intent (METIS versus Risk ranking) METIS = number of chemicals not clear Tier I Risk Ranking = 8707 chemicals Tier II Risk Ranking = ~50 case study chemicals	>760,000 chemicals • Amount of information varies by chemical
Curated?	No; meant to serve as a starting point for additional investigation of a chemical	Yes; various levels of curation depending on chemical

Toxicity information (qualitative)	• Limited to only classifying a chemical's carcinogenicity, mutagenicity, neurotoxicity, and reproductive toxicity
	  ○ Includes a citation for any classification
		• Limited to only classifying a chemical's carcinogenicity, reproductive toxicity, developmental toxicity, neurotoxicity, and endocrine disruption
		  ○ Includes a link to sources of any classification
		• Includes results for ToxCast (in vitro high through put assays that provide mechanistic information), if available

	NJRisk	Chemistry Dashboard
Toxicity values presented? (eg, RfD, CSF, etc)	No	Yes; if available for a chemical and provides links to source(s) • Provides reference values and cancer slope factors • Provide points of departure for various toxicities (reproductive, developmental, neurotoxicity, endocrine disruption) • Provides points of departures for various exposure durations (chronic, subchronic, acute, subacute)
Can be used to identify surrogate chemicals?	No	Yes; has 3 ways to identify surrogates • Provides a listing of "similar compounds" and "related substances" • Provides access to QSAR software (USEPA Toxicity Estimation Software tool) • Provides access to EPA's generalized read-across (GenRA) prediction module
Prioritize chemicals?	Yes • Risk rankings for chemicals could be used to inform the prioritization of a list of chemicals	Maybe • Data extracted from Chemistry Dashboard has been applied to prioritization frameworks developed by other agencies (MNDOH) • EPA is developing an interface that will allow for the prioritization of a list of chemicals, likely not available until fall of 2019
Physical information?	Yes	Yes
Environmental fate/transport?	Yes	Yes
Can conduct literature search?	No	Yes; once an initial search is conducted the user is given the option to search for literature via Google Scholar, PubMed, and PubChem