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Title: Reimagining Safe Drinking Water based on 21st Century Science

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Preface: Twentieth-century approaches to protecting drinking water supplies cannot keep pace with the ever-expanding set of chemicals that humans emit into the environment. However, with recent advances in bioassays, measurement of complex chemical mixtures, and artificial intelligence, we are on the cusp of developing a radically different approach to keeping our drinking water safe. In contrast to the reactive and piecemeal status quo approach, this new approach is proactive and evaluates drinking water quality more holistically by focusing on complex mixtures instead of a small set of regulated, well-known chemicals that have been studied for decades.

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Scientists estimate that humans produce tens of thousands of chemicals each year, with new chemicals developed every day.[1,2] Many of these chemicals enter drinking water supplies, often in complex mixtures that vary across space and time.[3] Yet even in the most institutionally advanced countries, regulations address only a small fraction of these chemicals and not until many years after they have appeared in drinking water. When regulations fail to match the scope and speed of changes in chemical pollution, they fail to fully protect people.

We can, however, completely change the way we keep our drinking water safe by leveraging advances in bioassays, measurement of complex chemical mixtures, and artificial intelligence. Rather than trying to isolate and address individual contaminants via a national list of regulated contaminants with well-known toxicities, we should instead focus on the entire chemical mixture in drinking water and offer system-specific engineering and policy solutions that are tailored to reducing overall health risks in the mixture. Importantly, these solutions can be developed even in the absence of scientific knowledge about every contaminant in the water. This Perspective describes how this future approach to protecting drinking water might look, contrasts it with the status quo, and identifies the scientific, economic, and regulatory challenges that must be addressed to bring it to fruition.

The status quo

Drinking water regulatory systems tend to be slow, piecemeal, and reactive.[4] In a world awash in chemicals, those attributes are obstacles to protecting human health. Consider, for example, per- and polyfluoroalkyl substances (PFAS), which are compounds used to produce non-stick coatings, water-repellent fabrics, and firefighting foams. Despite detection of PFAS in drinking water as early as 1984[5] and an estimated number of compounds exceeding 4,000,[6] the US EPA does not regulate PFAS in drinking water and only established lifetime health advisory levels for two PFAS in 2016: perfluorooctanoic acid and perfluorooctane sulfonate.

Although the regulatory focus on individual contaminants has improved public health, it is less appropriate in the modern chemical context. It not only ensures that most chemicals go unregulated, but it also can encourage solutions that may be no better, or even worse, than the original problems. For example, even though PFAS are not regulated in drinking water, the U.S. EPA's actions to limit the production of perfluorooctanoic acid and perfluorooctane sulfonate

incentivized manufacturers to switch to other PFAS, like GenX, which has a shorter chain-length than perfluorooctanoic acid and is also environmentally persistent and toxic.[7] Similarly, replacement chemicals for brominated flame retardants that are extensively used in plastics and electronics, such as organophosphates, have been shown to be of a similar or higher health concern than the compounds they replaced.[8] Preventing these regrettable substitutions[9] requires the development and implementation of alternative assessment strategies for chemicals.[10]

To safeguard drinking water, alternative strategies that move beyond a focus on individual contaminants are also needed when additive or synergistic effects among chemicals are relevant. For example, one could imagine drinking water contaminated with several chemicals that have similar toxicological pathways. Even if the concentration of each contaminant were below regulatory limits, the combined effect of the contaminants could rival or exceed the toxicological effect of single contaminant in a high concentration.[11]

Moreover, safeguarding drinking water requires addressing not only contaminants that are present in source waters but also contaminants that are formed within the drinking water supply systems, often as by-products of the applied treatment processes. A focus on eliminating regulated chemicals through water treatment often ignores that these processes can result in the formation of new unregulated chemicals.[12] For example, disinfection processes like chlorination have been shown to create more than 700 disinfection by-products (DBPs).[13] Yet few DBPs are regulated, and DBPs that are regulated are not the most toxic.[14] As such, regrettable substitutions in the drinking water context also comprise treatment processes and not just chemicals.

To handle growing numbers of chemicals in complex mixtures that vary over space and time, we need a regulatory system that is proactive and evaluates drinking water quality more holistically. We need a system that starts with the mixture, rather than one that only focuses on well-known chemicals that have been studied for decades and for which there is clear evidence of adverse health effects. We need a system in which toxicity of the environmental mixture is the primary focus because toxicity ultimately determines potential health impacts. Fortunately, scientists have already created key building blocks to develop such a system.

Recent scientific advances

Recent advances in bioassays, analytical chemistry methods, and computational approaches facilitate holistic evaluations of the potential risks in drinking water mixtures. To assess toxicity in complex mixtures, scientists have made substantial advances with *in vitro* and *in vivo* bioassays.[15,16] These bioassays have been primarily used to assess toxicity of wastewater,[17–19] in which contaminants are typically much more concentrated than in drinking water. However, enhancements in extraction methods and assay sensitivity now enable us to also assess drinking water quality.[20–23] Moreover, enhanced high-throughput capabilities for these bioassays have enabled the processing of large numbers of water samples and the testing of multiple biological endpoints, such as endocrine-disrupting effects, genotoxicity and mutagenicity.[24]

Once a bioassay detects bioactivity in a sample, scientists can leverage advances in analytical tools to identify the responsible chemicals. For example, in contrast to previous methods that detect and quantify a small set of known chemicals, newer non-target analytical methods enable the identification of large numbers of chemicals in complex mixtures.[25,26] These methods can be used as screening tools to obtain chemical signatures, or 'fingerprints,' of individual drinking water samples. These signatures shed light on the sources of the chemicals.[27] To identify the chemicals, scientists use search tools that compare the analytical data with information from online databases.[28–30] Although the number of chemicals in these databases is currently limited, it is rapidly increasing. The speed and scope of our ability to identify chemicals has been facilitated by the development of computational tools for predicting the physico-chemical properties of chemicals. If combined with *in vitro* bioassays (so called effect-directed analysis), non-target analytical methods can further be used to identify chemicals that are responsible for the observed toxic effects.[31–35] New computational tools further help predict toxicities based on the molecular structure of chemicals.[36,37] In addition to the evaluation of individual chemicals, these *in silico* approaches can also be used to assess toxicity of mixtures[38–40] and to help prioritize bioassay requirements for a comprehensive assessment of drinking water quality.[41]

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MiAMI

These advances give us tools that can radically change how we keep drinking water safe. This new framework for ensuring safe drinking water is called **MiAMI**, an acronym that captures its four essential components: Mixture, Assay, Measure, Innovate.

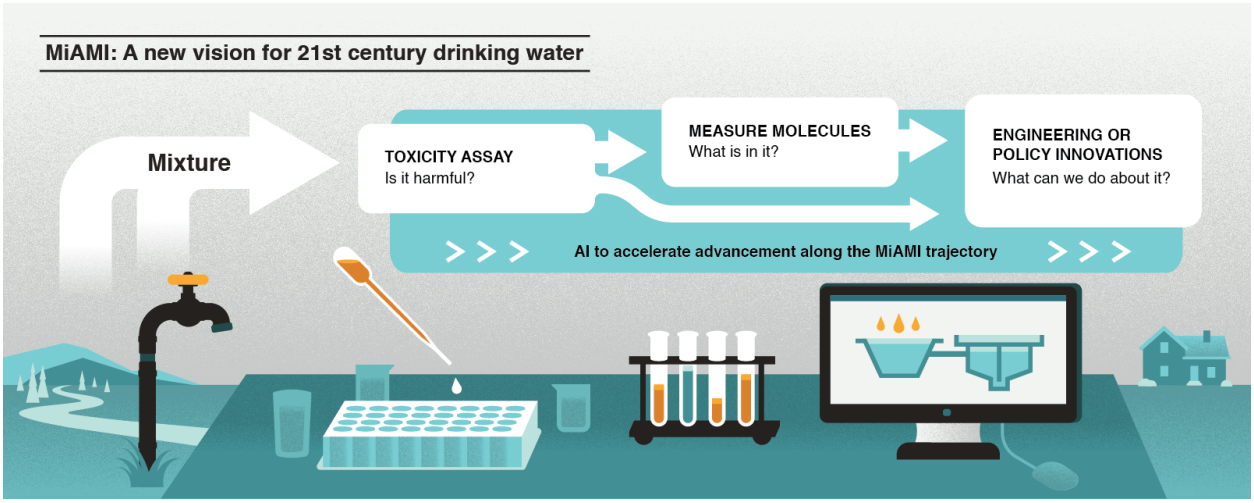

Fig. 1. MiAMI (Mixture, Assay, Measure, Innovate) Mixtures should be the starting point for assessing drinking water quality. Mixtures from a water system are first assessed for toxicity and composition. Then, building on laboratory and field-based rapid testing approaches, as well as predictive models driven by artificial intelligence (AI), engineering or policy solutions can be tailored to reduce overall health risks of the mixture. With advances in AI and rapid testing, one can go directly from Assay to Innovate. Multiple iterations of this cycle may be necessary to determine the best treatment solutions in a particular system.

Mixture and Assay

Rather than starting with individual contaminants, **MiAMI** starts with real-world mixtures from drinking water systems (Fig. 1) and assesses them for their cumulative toxicity. As noted above, focusing on a single contaminant often encourages substitutions to chemicals or treatment processes that are no less toxic than the target contaminant. Banning entire classes of chemicals or treatment processes may thwart such substitution[42] but can unnecessarily raise economic costs by banning substances or processes that are not as harmful as the target contaminant. The focus

on mixtures also acknowledges the formation of potentially toxic chemicals during the treatment processes.

Similar to how doctors approach their patients, **MiAMI** does not start with an inventory of known contaminants but rather with a diagnosis of an individual water system's health. Is a water system's mixture presenting indicators of "sickness"? As in medicine, standards that define "sickness" will need to be developed, but, as explained in the next section, other aspects of the analogy with healthcare also apply.

Measure

If bioassays indicate bioactivity in a pathway of concern, the next step is to determine which contaminants are responsible. This measurement is facilitated by innovations in mass spectrometry and other 'omnibus' analytical methods (e.g., non-target analytical methods), which allow one to characterize the composition of the entire mixture. Knowing the composition supports the generation of hypotheses about the causes of bioactivity, the sources of the causal agents, and the solutions that can reduce the bioactivity. However, as we discuss in the next subsection (*Innovate*), knowing the composition is not required for action; in other words, one can go straight from Assay to Innovate, skipping the Measure step.

Innovate

MiAMI seeks to map the assay and measurement outcomes to innovative solutions. Solutions to reduce toxicity can be implemented at different scales and include: (i) engineering solutions that remove contaminants in source water; (ii) engineering solutions that minimize toxic byproduct formation during drinking water treatment and in the distribution system;[43] (iii) engineering solutions, including prospective chemical design, that remove contaminants at the source; (iv) legal rules that ban contaminant production or its use; and (v) market mechanisms (e.g., environmental taxes) that increase the costs to produce, use or emit a contaminant, or an entire class of contaminants.[42] The choice of scale requires an analysis of the scope of the problem (e.g., do many drinking water systems have similar toxicity-contaminant profiles?) and the costs of addressing it at different scales. After solutions are applied, mixtures are analyzed again for

toxicity. Should the toxicity remain or shift (e.g., due to formation of by-products), the **MiAMI** steps are repeated until the toxicity is mitigated.

The search for innovative solutions is facilitated by artificial intelligence (AI), which excels at using data to make accurate predictions. Given a toxicity profile and a contaminant profile, AI can predict which contaminants are the most likely causes of the toxicity.[44] Given those predicted culprits, AI can also predict which engineering or regulatory solutions are most likely to eliminate the toxicity. Using data from iterations of the **MiAMI** steps, the algorithms will become more accurate over time. In fact, with richer data and more accurate algorithms, it may be possible to skip the Measure stage and proceed directly from Assay to Innovate (e.g., given a toxicity profile, AI predicts solutions without knowing the contaminants). The Measure stage can also be skipped by using small-scale, rapid testing of treatment options; i.e., the toxic mixture undergoes a battery of small-scale treatments, and the treated mixtures are sent back to the Assay stage for assessment.[45]

Precision drinking water protection

Although **MiAMI** can point to solutions that can be implemented at national and regional scales (e.g., a ban on a class of contaminants), **MiAMI** is particularly suited to identifying solutions at the level of water systems or systems of water systems. At that scale, **MiAMI** is patterned after the advances and aspirations in precision (individualized) health.[46]

Precision health promises better diagnoses, proactive interventions, and customized, more efficient treatments. In traditional medicine, a patient is treated as a set of separate diseases or risk factors, each of which is addressed separately, often with a one-size-fits-all therapy. In contrast, precision health leverages patient information and diagnostic tools to treat the patient holistically with a tailored intervention.

MiAMI takes an analogous approach to address water quality issues that are specific to individual water systems (Table 1). Like traditional medicine, traditional water regulations treat their patients with a fragmented approach. In contrast, precision health and MiAMI take more holistic approaches. Precision health envisions a more efficient and cost-effective healthcare system and **MiAMI** envisions a more efficient and cost-effective drinking water system, which

179 includes the protection of source waters. Furthermore, in the same way that precision health
180 recognizes that patients are highly heterogeneous in the factors that affect their health, MiAMI
181 recognizes that drinking water systems are highly heterogeneous in the factors that affect their
182 water quality. In the drinking water context, these factors include both natural and anthropogenic
183 sources of chemicals and the treatment processes used by the systems.

184 **Table 1.** Analogues between precision health and MiAMI

	Precision Health	**MiAMI**
Focus of care	Patients	Water systems
Disease	Perturbation of physiological systems	Contamination of drinking water
Caregivers	Health professionals	Policy makers & environmental professionals
Big Data	Clinical, genomic and other 'omic', social and behavioral data	Bioassay, mass spectrometry and multi-omics data; engineering models, field testbeds and observational data
Computational Tools	Machine learning/AI; systems modeling of biological networks	Machine learning/AI; bioactivity and engineering treatment modeling
Intervention Strategies	Therapies tailored to patient	Treatments tailored to water systems
Bottom-up Focus	Patients take active roles in their healthcare	Water systems and their community stakeholders take active roles in their drinking water supply

185

186 **Challenges for MiAMI**

187 Although the foundation for implementing **MiAMI** exists, there are scientific, economic, and
188 regulatory challenges that must be addressed to bring its vision to fruition.

189 *Scientific needs for implementing MiAMI*

190 The feasibility of **MiAMI** is supported by studies that have combined some of its components to
191 assess water quality. For example, scientists have evaluated the performance of advanced
192 wastewater technologies, such as ozonation and activated carbon filtration, by combining data on

the presence and formation of specific chemicals with data on toxicological effects determined by a battery of *in vitro* and *in vivo* bioassays.[47–49] Scientists have also evaluated the efficacy of different drinking water treatment systems by combining target analyses, non-target screening and effect-based monitoring.[35]

Nevertheless, just as achieving the full potential of precision health requires scientific advances, achieving **MiAMI**'s full potential requires advances in bioassays, analytical tools, rapid testing of treatment options, and data management and predictive analytics.

To use bioassays as the starting point for a new regulatory system, we will need high-throughput bioassay batteries that cover a wider spectrum of toxicological end points, as well as risk indices and action thresholds for these end points that are scientifically defensible.[26,50,51] We will also need assays with greater sensitivity and reproducibility, as well as methods that permit more efficient sampling and extraction (e.g., hydrophilic compounds).[52] These advances are not purely scientific. First, they will require coordination among scientists, regulatory agencies, and other stakeholders to set standards for assay use in the drinking water context. Second, they will require that the different stakeholders have confidence in these standards.

To leverage these advances in bioassays, we need advances in analytical methods. With more advanced effect-directed analyses,[53] we could greatly narrow down the set of candidate chemical compounds in mixtures that fail the bioassay stage. Similarly, 'omics' technologies such as metabolomics and transcriptomics could help identify effects of complex mixtures at the molecular level.[54–56] Recent advances in reactivity-directed analytical approaches also provide new opportunities to identify toxicants in complex mixtures by investigating their covalent binding to biomolecules, so called *in chemico* assays.[57] To further aid the identification of toxic contaminants, we need better predictive models of toxicity – specifically models that consider a contaminant's entire three-dimensional structure. In addition, we need to adapt current measurement strategies, which are best suited for hydrophobic chemicals, to detect the growing number of hydrophilic (polar) compounds.[7,52]

To minimize the period during which people are exposed to contaminants, we further need to develop strategies that enable the rapid testing of treatment options, ideally on-site and inexpensively. One example of such an approach is Rapid Small-Scale Column Testing

(RSSCT), which has been used to assess the effectiveness of activated carbon in removing contaminants from drinking water.[45]

As advances are made, they will not only more closely link bioassays (effect analysis) and analytical methods (exposure analysis). They will also generate large amounts of data, which regulators can further exploit to more effectively identify contaminants, more quickly innovate and create solutions, and more accurately predict adverse effects from proposed solutions prior to scaling them up. Exploiting this data deluge will also require water utilities and industry to deposit their data in central repositories (see, for example, California's new Open and Transparent Water Data Platform). These groups must believe that participation in the data repositories will translate into better outcomes for them, with minimal risks to reputations and bottom lines. Addressing water quality at the tap (i.e., contamination between the treatment plant and the consumer's tap) and in unpiped systems (e.g., wells) will require bringing consumers into the MiAMI system; in other words, encouraging consumers to have their tap water tested and allow their data to be deposited in central repositories. The development of these data repositories should be guided by FAIR Principles (guidelines aimed at improving the Findability, Accessibility, Interoperability, and Reuse of digital assets), although how best to follow these principles continues to be debated.[58]

Finally, scientists and regulators must work out an ontology for connecting disparate data on toxicity (bioassays), chemical structure (measures), and solutions (engineering and policy innovations). Fortunately, to create this ontology, we can draw on precision health's developments in database construction and management.[59]

Costs of implementing MiAMI

Although MiAMI can reduce the adverse health and environmental impacts associated with contaminated drinking water,[60] those reductions may require additional expenditures. Testing mixtures, treating contaminated water, and protecting source waters costs money, and any additional costs from implementing MiAMI need to be considered along with the additional benefits.

The costs of testing water samples under MiAMI will likely be higher than the costs of testing under the status quo approach, at least initially. However, this cost comparison ignores the fact

that MiAMI addresses environmental mixtures containing many more contaminants than those assessed under the status quo system. If one were to compare testing costs under MiAMI to testing costs of an extended status quo system that effectively manages tens of thousands of potential contaminants, MiAMI has clear cost advantages by obviating the need to identify and assess all contaminants in order to protect human health. Moreover, MiAMI's costs are likely to decline with advances in bioassay development, AI, and rapid tests of treatment technologies.

Because MiAMI will reveal heretofore unknown problems in drinking water mixtures that may require new treatments or rules, the costs of treating water or protecting source waters under MiAMI may be higher than they are in the status quo. Even when costs are not higher, they may be perceived as being higher because the status quo ignores the health costs of unknown and unaddressed contaminants in drinking water systems; in other words, the status quo may seem cheaper, but only because a full assessment of its costs is impossible when regulators are ignorant about the potential threats in drinking water mixtures.

Rather than encourage continued ignorance to minimize the costs of protecting drinking water, a superior approach would be to make the benefits and costs of action explicit – the treatment costs as well as the benefits to health and environment. Then one can directly assess the benefit-cost tradeoffs associated with different treatment options (e.g., extending the approach of Allman et al.[61] to answer the question, "For a fixed budget, which bioassay results should be improved and by how much?" or, equivalently, "For a specific bioactivity threshold, which treatment option minimizes cost?").

The last, and potentially most important, additional costs to implementing MiAMI are the costs to those who have a stake in the status quo system. Drinking water suppliers have invested in processes and technologies that work within the status quo system. Testing labs are set-up to test for contaminants on a regulatory list. Research labs are oriented towards identifying and thoroughly elucidating individual contaminants one at a time. After widescale adoption of the MiAMI approach, the operations of these stakeholders will need to change, and that change may be resisted, particularly if it creates new economic winners and losers.

Given the potential for additional costs under MiAMI, one might expect that MiAMI would be less appropriate for financially constrained drinking water systems in small communities

throughout high-income nations, as well as in both small and large communities in low and middle-income nations that are already unable to address well known contaminants. Yet with advances in bioassays, these communities may find it cheaper to assess their drinking water problems under MiAMI than under the status quo. MiAMI does not solve the financial constraints to adopting solutions that these communities face, but with advances in AI, it may provide these systems with more useful information about where their problems lie. In the short term, however, financially constrained systems may find it optimal to simply focus on addressing the known contaminants in their systems and adopting best practices for their peer cohort.

Transforming Science into Regulations

The status quo system, by focusing on individual contaminants rather than toxicity in an aqueous mixture, does not require anyone to address thorny issues about how to operationalize, in a regulatory setting, a mixture-focused approach to protecting drinking water. Under MiAMI, however, these issues must be addressed.

Providing a roadmap for moving from the results of bioassays to regulations is beyond the scope of this brief Perspectives article. Yet, as noted in the "*Scientific needs*" subsection, such a roadmap is necessary to make MiAMI a reality and its development will require coordination among scientists, regulatory agencies and other stakeholders. Recent efforts to provide an analogous roadmap in the context of the Toxic Substance Control Act (TSCA) indicate that developing a roadmap for MiAMI will require substantial investments from the scientific and regulatory community.[62] "Toxicity" is a multi-faceted construct that has a complicated mapping to concentrations and composition of contaminants. For example, toxicity risk can arise from single exposure events or only after accumulated exposure, and it can depend on average concentrations, maximum concentrations, or the variance of concentrations. Simply because a mixture triggers a response in a bioassay does not mean it will have a deleterious health effect (not does the lack of a response imply the absence of such an effect).[63–65]

Under MiAMI, ambiguity about what the scientific evidence means for human welfare will remain and the regulatory system will continue to have to make decisions under this ambiguity. Just as scientists, regulators and other stakeholders argue over how to interpret laboratory tests on animals or epidemiological studies on humans, they will argue over how to interpret tests on

cells or cells on chips. Debates will also arise about how to translate bioassay test results into cost-benefit analyses. Moreover, in contrast to the status quo approach of addressing risks chemical by chemical, MiAMI, with its emphasis on assays and AI, has a "black box" aspect to it that may further exacerbate perceptions of ambiguity about the evidence among scientists and regulators. To reduce that ambiguity, we can draw on recent advances in improving AI model interpretability.[66]

Despite these sources of ambiguity, the way in which MiAMI combines biological, chemical and data analytic evidence may eventually allow scientists and regulators to more easily triangulate among sources of evidence. Moreover, evaluating the success of treatment options may be more straightforward under MiAMI where the elimination of negative bioassay responses, or trends in the desired direction, may be sufficient for quantifying the overall impact of a treatment innovation. Lastly, MiAMI can contribute to broader chemical regulation efforts when the application of omnibus analytical methods to large data sets of drinking water mixtures leads to widespread detection of specific anthropogenic chemicals that are of health concern.

The way forward

We are on the cusp of developing a radically different approach to keeping our drinking water safe – an approach that is water system-specific and proactive, rather than reactive. This new approach, called **MiAMI**, leverages existing information on toxic chemical contaminants, new information that comes from advances in the application of bioassays and analytical methods, and new diagnostic tools, such as predictive algorithms based on AI. The building blocks for **MiAMI** already exist but realizing this vision will require government-scientist partnerships and integration across chemistry, biology, computer science, statistics, law, and economics. Such partnerships and integration are very much within our grasp.

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