of people who are too unwell to continue in direct participation. Association with these health records can additionally allow investigation of longitudinal changes, differences in age of diagnosis, and multimorbidity (the simultaneous presence of two or more chronic diseases in a person). However, health data in electronic records do suffer from missing information, having bias of reporting, and are subject to differences in health care systems across countries, which poses a major challenge to their use in genomic analyses (*10*, *11*).

Broad assessments that include genetic data and thousands of phenotypes likely still miss some true-positive gene-trait associations. Therefore, follow-up with tailored approaches that use refined phenotype definitions—which take into account other disease diagnoses or medication use, for example—are still needed, such as excluding individuals on diabetes medication or with red blood cell disorders when assessing the amount of hemoglobin A1c present. Further, integration of molecular traits, such as proteomics, from diverse populations will increase understanding of the mechanisms underlying gene-disease associations.

The global scientific community has a duty to ensure increased global representation in genomic studies and therefore equity in benefit from genomic advances (*8*, *12*). Beyond improved representation of genetic ancestry, representation across other demographics such as sex, gender, and age should be considered. Verma *et al.* report that participants of the Million Veteran Program are older in age as compared with the general population, and only 8% are female. Therefore, the data limits studies to conditions that are specific or more prevalent in females or in younger individuals. Nevertheless, these data provide a valuable complement to other large-scale biobank efforts and highlight the benefit of including more diverse populations in genomic discovery. ■

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CHEMISTRY

From "forever chemicals" to fluorine-free alternatives

Identifying alternatives to PFAS requires weighing trade-offs and uncertainties

By **Mohamed Ateia**[1,2] *and* **Martin Scheringer**[3,4]

Per- and polyfluoroalkyl substances (PFAS) are a large group of more than 10,000 synthetic chemicals widely used for providing heat, water, oil, and stain resistance in applications such as nonstick coatings, firefighting foam, and food packaging. These "forever chemicals" are hazardous for human health and the environment, motivating efforts to find suitable replacements (*1*). The concerns surrounding PFAS are particularly serious because of their unusual persistence and widespread use, resulting in the contamination of both indoor and outdoor environments. Transitioning to PFAS-free alternatives requires careful evaluation of trade-offs as well as accounting for uncertainties to determine the most effective short- and long-term research and development strategies.

Recent regulatory actions and legal settlements have accelerated the search for PFAS-free alternatives. The US Department of Defense, for example, ceased procuring PFAS-containing aqueous film–forming foams (AFFFs) in October 2023 and started listing fluorine-free foam in their qualified products database, following military specifications for F3 use in land-based and freshwater firefighting applications (*2*). The European Union is working on a plan to restrict the entire PFAS family in many applications after a proposal by the national authorities of Germany, Denmark, the Netherlands, Norway, and Sweden. The US Environmental Protection Agency (EPA) has set limits on six PFAS in drinking water and has designated two of them as hazardous substances under the Superfund law as part of the agency's PFAS Strategic Roadmap. Chemical manufacturers Chemours, DuPont, and Corteva also agreed to multibillion-dollar settlements related to PFAS pollution. Separately, a recent ChemSec report estimated the annual global economic costs of PFAS at $16 trillion, identifying 12 major producer companies. Among them, 3M plans to end all PFAS production by 2025. Overall, heightened health and liability concerns are propelling a large-scale transition to PFAS-free alternatives (*3*). However, past experiences have shown that replacing chemicals with alternatives to reduce harm can result in unintended consequences and regrettable substitutions, as seen with the harm to human health caused by dry-cleaning solvents and chemicals used to manufacture plastics (i.e., bisphenol A and phthalates).

The transition away from PFAS has already occurred in some sectors, such as textiles, food packaging, cosmetics, and electronics manufacturing. However, completely phasing out PFAS while also avoiding regrettable substitutions still requires substantial additional efforts. The specific combination of problematic physicochemical properties (including extreme persistence and low removability from water), extensive and long-term exposure of humans and the environment, and a complex societal reliance on these chemicals presents formidable challenges (*4*). Therefore, addressing these challenges requires a comprehensive scientific understanding that incorporates the intricate relationships between PFAS uses, exposure pathways, and societal implications of the transition (see the figure).

Standard hazard assessment protocols often overlook the most concerning attributes of PFAS because they concentrate on bioaccumulation and acute effects rather than the extraordinary longevity and the impact of chronic low-dose exposure. Through numerous diverse uses in sectors such as surface treatment, firefighting, aerospace, and medicine over many decades, PFAS have permeated ecosystems and human lives globally (*5*). Their unparalleled persistence enables accumulation across generations with little natural degradation. Persistence on this scale means that pollution will linger substantially longer than over the few decades that conventional risk evaluations consider. Additionally, the chronic toxicity of many PFAS presents long-term health risks even at the

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low concentrations encountered in daily life. This impact is underaccounted for by short-term damage measurements (*6*). The ubiquity in the environment also raises questions of mixture effects that are currently underexplored. The multistressor aspects of PFAS toxicity, including effects on the immune system and the overall resilience of organisms to chemical and other agents, challenge current assessment frameworks.

Replacing PFAS effectively in the large number of diverse applications necessitates avoiding fragmentation of the assessment and replacement activities. Although targeted assessments and identification of the most important uses are needed, losing sight of the overarching goal to minimize exposure and risks could stall progress. Therefore, evaluations of PFAS-free alternatives should be maintained under a comprehensive phaseout blueprint or overall plan to circumvent piecemeal discussions in isolated sectors. Because of the vital role of PFAS in modern technologies, enhancing the resilience of the supply chain by developing PFAS-free alternatives that incorporate robustness and redundancy is crucial. This approach will help mitigate infrastructure dependencies and navigate complex global networks effectively (*7*). Thus, achieving progress in replacing PFAS necessitates implementing strategies that focus on reducing persistence while also incorporating realistic evaluation time frames that align with human health considerations. Only through comprehensive research that jointly investigates the roles and functions of PFAS in important applications can the chances of sustainable PFAS-free solutions be maximized.

One likely consequence of the surge in demand for products that minimize exposure to PFAS is an increasing rate at which new PFAS replacements are introduced to the marketplace for different uses (*8*). Ultimately, the slight advantage of PFAS in certain performance metrics pales in comparison with the consequences of inaction. Yet, an acceptable balance between functionality and protection of human health and the environment depends on incorporating principles of green chemistry along with a design strategy that takes into account everything from manufacturing to disposal (*9*). Open data sharing platforms present an opportunity to reduce duplication in the information-gathering effort worldwide, specifically related to PFAS emissions, uses, alternatives, and related aspects. Democratizing datasets and making them accessible across industry, government, and academia should maximize the collective knowledge on the availability and performance of PFAS-free alternatives. This fact-based dialogue and data exchange need to be accomplished while balancing out the protection of intellectual property. Complementing design-driven substitution with long-term computational modeling could help preemptively identify options that pose minimal future health and environmental issues while fulfilling needs (*10*).

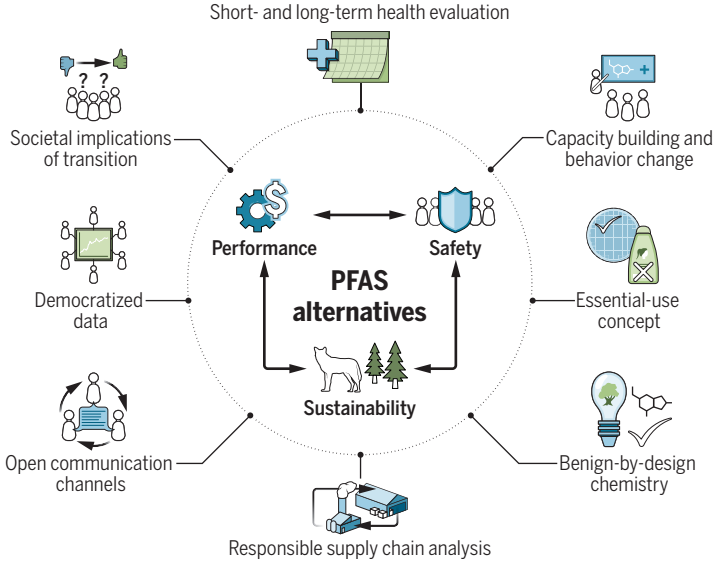
Many industries already recognize that a world without PFAS is achievable. For example, major manufacturers in clothing, furniture, cosmetics, and other sectors have started phasing out PFAS, demonstrating that using PFAS is not essential to their business models. However, the situation is more complicated in the production and uses of fluoropolymers and in the semiconductor industry because of the demanding conditions and diverse applications of PFAS (*8*). Broad assessments of chemical or nonchemical alternatives in process and product design are necessary because of the many interlinked processes involving different PFAS uses, such as construction, aerospace, and electronics. PFAS-based materials are used in construction for waterproofing, sealants, and fire-resistant coatings. In aerospace, they are used in wiring insulation, hydraulic systems, and fuel seals. Similarly, the electronics industry relies on PFAS for circuit boards, connectors, coatings, and adhesives. Despite ongoing research and development, it remains unclear how widely alternatives are being adopted by manufacturers and to what extent the market still relies on PFAS-based processes. An overarching framework is essential to provide structure, but flexibility is also key.

With input on essential uses and exposure prioritization, sector recommendations can steer the way toward safer alternatives (*11*). A prime example is 3M's development of a fluorine-free foam (F3) in 2003 that challenged the notion that PFAS were irreplaceable in firefighting applications. PFAS-containing AFFFs are highly effective because they create a continuous film over the fuel surface, suppressing vapors and extinguishing fires rapidly. This film formation is a distinctive property of PFAS that has proven difficult to replicate (*2*). By contrast, F3 formulations do not form such a film and rely primarily on a bubble blanket to contain fuel vapors, and their performance is more dependent on foam quality, such as aspiration and expansion ratios. Progress in F3 offers a crucial advantage by reducing environmental and long-term health impacts without compromising fire-suppression capabilities.

Progress inherently demands weighing trade-offs and uncertainties. Prioritizing accurate scientific evaluations over rhetoric and cooperation over defensiveness will be essential for the transition to safer alternatives (*12*). In this regard, several responses to the PFAS phaseout discussion by PFAS manufacturers have revealed three actions that should be avoided. This includes exclusively emphasizing the advantages of PFAS because doing so overlooks well-established health and environmental concerns. The profile of properties alone should not be the overriding factor in evaluating the use of PFAS. Another point is denial of the clear links between PFAS exposures and impacts. Claiming that no harm has been proven ignores evidence that increasingly points to risks even at very low levels of exposure (*1*, *13*). Finally, exaggerating the consequences of eliminating PFAS use without evidence should also be avoided. This includes predicting a technological disaster or asserting that alternatives pose a threat to technological progress, such as the energy transition that is vital for mitigating

PFAS alternatives require assessing trade-offs

Per- and polyfluoroalkyl substances (PFAS) replacements need to balance the performance for industry with chemical safety and sustainability to avoid adverse environmental and health outcomes. An ideal PFAS replacement has effective functionality, minimal safety issues, and a minimal environmental footprint. Finding long-term and safer alternatives requires a range of considerations (outside the dotted circle) for responsible design.



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climate change. Responsible solutions to the problem of pervasive PFAS uses require acknowledging both immediate and long-term impacts through life cycle analysis frameworks. A strategy that takes into account both timescales ensures that PFAS-free alternatives will avoid unintended issues while meeting essential needs.

For alternatives to PFAS, setting realistic expectations is important. Not all substitutes may immediately match the performance of well-established chemicals that have been optimized over decades of use (*14*). However, these differences do not outweigh the enormity of risks posed by PFAS and the large cost of remediating widespread contamination. Transitioning away from PFAS requires some trade-offs, at least temporarily, until alternative solutions can be further refined. Giving appropriate weight to health, safety, and environmental stewardship means that such compromises are necessary. With collaborative research and development, performance gaps will narrow over time, just as they have for many other regulated chemicals. Meanwhile, uses where adequate substitutes already exist should transition rapidly. Remaining applications can buy time through risk-reduction measures while innovation occurs. Continuing the widespread use of PFAS can no longer be justified given the consequences. Moving forward will take open-minded problem-solving and willingness to accept a diversity of different solutions (*15*). ■

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MEDICINE

The benefits of GLP-1 drugs beyond obesity

Glucagon-like peptide–1–based medicines have weight loss–independent actions

By **Daniel J. Drucker**

Glucagon-like peptide–1 (GLP-1) is secreted from gut endocrine cells in response to food ingestion and acts as an incretin hormone to potentiate glucose-dependent insulin secretion. Pharmacological GLP-1 receptor (GLP-1R) activation reduced glucagon secretion (which raises blood glucose) and gastric emptying, leading to the development of GLP-1 therapies for the treatment of type 2 diabetes (T2D). GLP-1R is expressed on several pancreatic islet cell types and within multiple regions of the central nervous system. Subsequent studies revealed that exogenous GLP-1 administration inhibited food intake through brain GLP-1R activation in animals and humans, leading to weight loss. The decades-long use of GLP-1 medicines, principally acylated peptides such as liraglutide and semaglutide, for the treatment of obesity and T2D (*1*) has revealed that they also exert pleiotropic actions beyond glucose and weight control, such as reduction of heart and kidney diseases. There are several potential mechanisms underlying these benefits, such as reducing systemic inflammation (*2*), which have implications for future clinical applications and drug development.

The first approved GLP-1 medicines, such as exenatide and liraglutide, required once- or twice-daily administration and were followed by longer-acting versions such as dulaglutide, exenatide once weekly, semaglutide, and tirzepatide [a glucose-dependent insulinotropic polypeptide receptor (GIPR) and GLP-1R coagonist] that are suitable for once-weekly administration. A major nonmetabolic benefit of GLP-1 therapies became evident in the cardiovascular system. A series of preclinical studies demonstrated that GLP-1R agonists protect ischemic myocardium and preserve cardiac function after ischemic cardiac injury, actions that are independent of glucose control or weight loss (*1*). GLP-1 medicines were studied in eight distinct cardiovascular outcome trials in people with T2D, and one trial in people with obesity. Long-acting GLP-1 medicines that are continuously present in the circulation reduced rates of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death in people with T2D and/or obesity. Subsequent trials demonstrated a benefit for semaglutide in people with heart failure with preserved injection fraction, with or without T2D (NCT04788511).

How might this happen? Indirect roles for the cardiovascular benefit of GLP-1 drugs include reduction of blood pressure and attenuation of atherogenic lipoproteins secreted from the gut, better control of blood glucose, and weight loss. However, preclinical studies demonstrate that GLP-1 protects the ischemic heart in normotensive nondiabetic animals to a greater extent than achieved with weight loss. Furthermore, a long-acting GLP-1 therapy, albiglutide, withdrawn from the market owing to modest efficacy for reduction of glucose and body weight in people with T2D, reduced the rates of major adverse cardiovascular events by 22% (NCT02465515).

Mechanistically, the distribution of GLP-1R expression differs in the mouse versus the human heart, challenging the utility of preclinical studies for inferring underlying mechanisms in humans. GLP-1 therapies also reduce the development of atherosclerosis in sensitized mouse models, and clinical trials are underway in people with peripheral artery disease (NCT04560998). The mechanisms linking GLP-1R activation to the reduction of atherosclerosis and/or improved blood flow are not well understood but may be independent of weight loss and are instead associated with reduced inflammation. Interestingly, the cardioprotective effect of semaglutide observed in people with obesity developed within months of drug initiation, well before meaningful weight loss had been achieved in most trial participants. Furthermore, in the SELECT cardiovascular outcome trial (NCT03574597) studying semaglutide in people with obesity, the extent of weight loss did not correlate with the effects of the drug to reduce heart attacks, stroke, and cardiovascular death. Whether GLP-1 medicines might be cardioprotective in people with type 1 diabetes, or nondiabetic individuals at

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