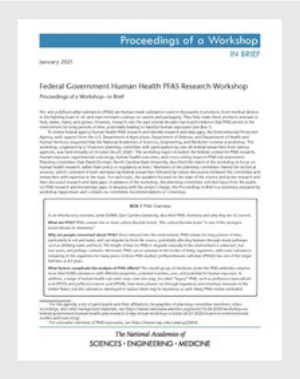

Federal Government Human Health PFAS Research Workshop: Proceedings of a Workshop—in Brief (2021)

DETAILS

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Proceedings of a Workshop

IN BRIEF

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Federal Government Human Health PFAS Research Workshop

Proceedings of a Workshop—in Brief

Per- and polyfluoroalkyl substances (PFAS) are human-made substances used in thousands of products, from medical devices to fire-fighting foam to oil- and stain-resistant coatings on carpets and packaging. They help make these products resistant to heat, water, stains, and grease. However, research over the past several decades has found evidence that PFAS persist in the environment for long periods of time, potentially leading to harmful human exposures (see Box 1).

To review federal agency human health PFAS research and identify research and data gaps, the Environmental Protection Agency, with support from the U.S. Department of Agriculture, Department of Defense, and Department of Health and Human Services, requested that the National Academies of Sciences, Engineering, and Medicine convene a workshop. The workshop, organized by a 10-person planning committee with participation by over 60 federal researchers from various agencies, was held virtually on October 26–27, 2020.[1] The workshop topics included: the federal context for PFAS research, human exposure, experimental toxicology, human health outcomes, and cross-cutting issues in PFAS risk assessment. Planning committee chair David Dorman, North Carolina State University, described the intent of the workshop to focus on human health research, rather than policy or regulatory actions.[2] Members of the planning committee chaired the technical sessions, which consisted of brief overviews by federal researchers followed by robust discussions between the committee and researchers with expertise in the topic. For each topic, the speakers focused on the state of the science and active research and then discussed research and data gaps. In advance of the workshop, the planning committee solicited input from the public on PFAS research and knowledge gaps. In keeping with the project charge, this Proceedings in Brief is a summary prepared by workshop rapporteurs and contains no committee recommendations or consensus.

BOX 1 PFAS Overview

In an introductory overview, Jamie DeWitt, East Carolina University, described PFAS chemistry and why they are of concern.

What are PFAS? PFAS contain one or more carbon-fluoride bonds. This carbon-fluorine bond "is one of the strongest bonds known in chemistry."

Why are people concerned about PFAS? Once released into the environment, PFAS remain for long periods of time, particularly in soil and water, and can migrate far from the source, potentially affecting humans through many pathways such as drinking water and food. The length of time for PFAS to degrade naturally in the environment is unknown, but lasts years, and perhaps centuries. Moreover, PFAS can accumulate in the bodies of living organisms, with some substances remaining in the organisms for many years; of those PFAS studied, perfluorohexane sulfonate (PFHxS) has one of the longer half-lives at 8.5 years.

What factors complicate the analysis of PFAS effects? The overall group of chemicals under the PFAS umbrella comprise more than 9,000 substances with different properties, potential toxicities, uses, and potential for human exposure. In addition, a range of human health outcomes may come into play. So-called "legacy" PFAS, such as perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), have been phased out through regulatory and voluntary measures in the United States, but the substances developed to replace them may be hazardous as well. Many PFAS remain unstudied.

[1] For the agenda, a list of participants and their affiliations, biographies of planning committee members, video recordings, and other background materials, see https://www.nationalacademies.org/event/10-26-2020/workshop-on-federal-government-human-health-pfas-research-2-day-virtual-workshop-october-26-27-2020-board-on-environmental-studies-and-toxicology.

[2] For a broader overview of PFAS exposures, see https://www.nap.edu/catalog/25856.

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CONTEXT AND PRIORITIES FOR PFAS HUMAN HEALTH RESEARCH ACROSS FEDERAL AGENCIES

Representatives of federal agencies with interest in PFAS shared the context and priorities for PFAS human health research. Several participants stressed that beyond each agency's specific programs summarized below, federal researchers are actively engaged in coordinating efforts and sharing knowledge with each other and the broader scientific community.

> *"PFAS are among the most persistent organic pollutants that we have ever discovered. ...We have yet to discover how long it will take PFAS to degrade naturally in the environment."*
> *– Jamie DeWitt, East Carolina University*

Environmental Protection Agency (EPA)

PFAS is one of EPA's highest priorities, reported David Dunlap. EPA is committed to conducting research to understand and prioritize risks to public health and the environment to help inform the agency's management decisions. In 2018, EPA created a first-of-its-kind PFAS action plan,[3] and the agency supports a comprehensive PFAS research program to understand and inform responses to PFAS risks. EPA decision making, such as protecting drinking water, designating hazardous substances, and regulating new and existing chemicals, benefits from human health PFAS research from EPA and other agencies. Dunlap described near-term EPA research priorities, such as completing seven ongoing PFAS toxicity assessments, developing class-based approaches to PFAS risk assessment, and understanding human exposure levels and pathways. Longer-term EPA priorities include how to account for PFAS mixtures, understand impacts on vulnerable subpopulations, and understand the totality of exposure pathways, including inhalation and dermal exposures.

U.S. Department of Defense (DoD)

Jody Wireman stated that DoD has used PFAS-containing aqueous film-forming foam (AFFF) to manage petroleum-based fires since the 1970s. As the health impacts of AFFF have become known, DoD has worked to understand and mitigate or eliminate potential PFAS exposure by its personnel, their families, and communities near DoD facilities. In 2019, DoD created a task force to mitigate and eliminate the use of current AFFF, understand PFAS exposures and potential impacts, and fulfill clean-up responsibilities related to PFAS releases. DoD collaborates with multiple partners on human health research, including exposure assessments and public health studies at sites with PFAS-contaminated drinking water near current or former DoD installations. The military's public health and environmental centers are conducting toxicology and pharmacokinetic modeling studies for PFAS and PFAS-free AFFF. In addition, the Strategic Environmental Research and Development Program (SERDP) supports research on PFAS sampling and analysis, fate and transport, and ecotoxicology.

Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry (CDC/ATSDR)

Patrick Breysse explained that the Agency for Toxic Substances and Disease Registry (ATSDR) is a consumer of PFAS research in its authorized mission to assess the presence and nature of health hazards from chemical releases and hazardous waste sites and also conducts public health assessments and exposure research where current information is incomplete. ATSDR's draft toxicological profiles, now under review, contain public health guidance on minimal risk levels for four PFAS, and CDC is collecting PFAS biomonitoring data across the country that serve as benchmarks across populations and over time. ATSDR is currently conducting public health assessments in over 40 communities, and exposure assessments are underway in 10 communities with contaminated drinking water. The ATSDR Multi-Site Health Study is also examining PFAS health effects in more than 2,000 children and 7,000 adults.

National Institutes of Environmental Health Research (NIEHS)

NIEHS, a center of the National Institutes of Health, focuses primarily on preventing disease and improving human health, explained Richard Woychik. The center conducts research on harmful chemicals and agents in the environment to inform actions to prevent exposure. NIEHS's ongoing research portfolio includes Superfund Research Program support for the Sources, Transport, Exposure and Effects of PFAS (STEEP) research program at the University of Rhode Island and the Center for Environmental and Human Health Effects of PFAS at North Carolina State University. NIEHS also supports a number of domestic and international epidemiological studies to measure the health effects of PFAS exposure. Work at the National Toxicology Program (NTP) within NIEHS includes research on the toxicity of PFOA, PFOS, and GenX.[4] Research is also underway in collaboration with DoD to identify safer alternatives to AFFF and with EPA to investigate the bioactivity of about 150 PFAS chemicals.[5]

[3] See https://www.epa.gov/pfas/epas-pfas-action-plan.

[4] GenX is a tradename for a technology used to manufacture fluoropolymers without PFOA. The major chemicals associated with GenX are hexafluoropropylene oxide dimer acid and its ammonium salt. See https://www.epa.gov/pfas/basic-information-pfas.

[5] See https://www.epa.gov/chemical-research/pfas-chemical-lists-and-tiered-testing-methods-descriptions.

Food and Drug Administration (FDA)

To ensure the safety of the U.S. food supply, FDA is developing analytical methods to quantitate PFAS in food and is conducting studies to understand whether foods are a significant source of PFAS exposure, said Susan Mayne. FDA has conducted eight surveys to measure specific PFAS in foods, including at sites with known contamination, and the Total Diet Study monitors for PFAS in commonly eaten foods that represent the average U.S. diet. Upon request, FDA assists states in analyzing the food supply in contaminated areas. FDA also monitors research on PFAS in food contact applications, such as cookware and packaging. In July 2020, after studies raised questions about the biopersistence of a specific subset of short-chain PFAS, FDA announced voluntary agreements to phase out sales of certain food-contact substances that contain or may be metabolized to 6:2 fluorotelomer alcohol.[6]

U.S. Department of Agriculture (USDA)

"Questions about possible PFAS contamination and persistence at all points in agricultural systems must be addressed as part of USDA's larger mission of ensuring safe food supplies and safe production environments," said Steven Kappes. The USDA Agricultural Research Service (ARS) research includes environmental fate and transport studies of chemicals and contaminants that originate on agricultural land or are transported to processing facilities. ARS and the Food Safety Inspection Service (FSIS) are developing tests and assessments of PFAS in crop and animal agriculture. FSIS recently developed a testing methodology for 16 different PFAS in livestock tissues and bovine plasma and conducted assessments of PFAS in cattle. Testing will soon expand to swine, chicken, and catfish.

United States Geological Survey (USGS)

USGS develops datasets and information by designing and implementing long-term research sites and monitoring networks, explained Michael Focazio. USGS research to understand the fate and transport properties of PFAS, including precursors,[7] can inform remediation and exposure mitigation. USGS is also working to fill gaps related to PFAS effects on ecosystems, including bioaccumulation, exposure, toxicity, and adverse outcome pathways to fish and wildlife, which may be relevant to humans. The agency is developing and using screening tools for precursor compounds, as well as nontargeted analyses and total organic fluorine methods to understand the occurrence of PFAS in the environment. Additional information on exposure, toxicity, and human-health benchmarks, combined with advances in analytical methods, will help the agency prioritize its future research.

National Institute of Standards and Technology (NIST)

NIST provides reference materials, reference data, and other tools that underpin laboratory measurements of PFAS, reported Benjamin Place. NIST can provide reference materials in various matrices, including human serum and plasma, that help laboratories determine PFAS exposure in humans. In collaboration with other agencies, NIST is developing reference materials for PFAS in AFFF formulations and in food and agricultural materials. NIST is also conducting research on PFAS exposure from firefighting gear and developing methods and validation strategies for nontargeted analysis.

U.S. Department of Transportation (DOT) Volpe National Transportation Systems Center

Chris Zevitas said DOT's Volpe Center provides expertise across environmental, occupational safety, and health compliance areas on emerging pollutants, including PFAS. Work focuses on environmental clean-up to address legacy contamination at transportation facilities where PFAS may have been released, particularly related to AFFF applications. Human health research is leveraged to identify potential contaminants of concern and pathways of human and environmental exposures and to develop clean-up goals and remediation strategies.

Federal Aviation Administration (FAA)

PFAS is of importance to FAA because AFFF is used during airport firefighting operations, according to Marc Tonnacliff. FAA is conducting research in partnership with DoD, other agencies, and private industry on potential replacements, including a chemical analysis with the Air Force Civil Engineering Command to identify products without PFAS or other emerging contaminants. FAA also has conducted research on ways to test AFFF systems without the need to discharge foam on the ground, which has led to policies and initiatives to reduce AFFF discharge at civil airports.

[6] See https://www.fda.gov/news-events/press-announcements/fda-announces-voluntary-agreement-manufacturers-phase-out-certain-short-chain-pfas-used-food.

[7] Precursor compounds are large PFAS molecules that break down in the environment into smaller PFAS, which are more typically monitored.

HUMAN EXPOSURE PATHWAYS AND MEASUREMENTS

In the first of the four science-based sessions, speakers and discussants focused on human exposure, encompassing biomonitoring, drinking water, diet, occupational exposures, and other pathways such as consumer products.

Biomonitoring

State of the Science: Antonia Calafat, CDC, highlighted PFAS biomonitoring findings, including surveillance of 13 legacy PFAS through the National Health and Nutrition Examination Survey (NHANES) from 1999 through 2016, which revealed universal exposure to several long-chain PFAS. Biomarkers—primarily blood levels of PFAS—are used as an integrated measure of exposure, given the variety of sources of PFAS exposure. For short-chain and replacement PFAS, biomonitoring has shown low detection frequencies and levels in both serum and urine. Although urine biomonitoring is sometimes used for contaminants with short half-lives, Calafat noted that current approaches to biomonitoring, including analysis of urine samples, may lack the sensitivity to detect these chemicals that are non-persistent and do not bioaccumulate. Newer analytical approaches are available to assess a broad suite of PFAS but have limitations.

Biomonitoring provides measurements of exposure at a certain point in time. Given the half-life of most PFAS are on the order of 2–4 years, David Savitz, Brown University, said biomonitoring provides a reasonable measure for prolonged recent exposure. However, without historical measurements, longer-term exposures cannot be accurately reconstructed, and it may not be possible to estimate exposure at the relevant time period before disease occurs. Additionally, biomarker levels may be affected by individual differences in metabolism, uptake, or excretion. Disease processes of concern may themselves alter human physiology in a way that affects biomarker levels, which is problematic for understanding PFAS effects. When there is no dominant source of environmental contamination, physiologic variations across individuals become more influential.

Active Research: Calafat described research underway to increase understanding of how specific exposures can contribute to body burden and harmonize biomonitoring practices across states. Ongoing research on nontargeted analyses may help identify new PFAS for biomonitoring,

Research Gaps and Discussion: Calafat noted the need to prioritize the most relevant PFAS for targeted biomonitoring using information from coordinated environmental monitoring programs. Planning committee member Kurunthachalam Kannan, New York University, pointed out that most biomonitoring studies focus on just 10 to 20 of the thousands of PFAS compounds, and some may not accumulate in serum where most biomonitoring measurements are made. Calafat concurred that newer forms of PFAS may require new, more sensitive methods of detection. She characterized nontargeted analysis as a "powerful tool for identification and for discovery," but with lower sensitivity than targeted methods. Total organofluorine methods have greater sensitivity than nontargeted analyses but are labor-intensive and difficult to scale up. Ideally, she suggested, nontargeted analyses would be used to identify new compounds, and subsequently standards and targeted analytical methods could be developed.

Calafat also emphasized the need to evaluate other approaches for exposure assessment, such as modeling, for short-chain and other alternative PFAS with short half-lives. James Smith, DoD, added, "toxicologically, the presumption is that the longer these compounds are resident in the body, the longer their half-life, the more toxic they are. We're not actually sure that's a good assumption to make at the moment, but it seems to hold true for many of the long-chain compounds." Knowledge about how long newer PFAS remain in the body and at what concentration, Smith said, can help determine "whether there's a concentration below which people are safe from exposure and above which we would have some concern."

Drinking Water

State of the Science: According to Susan Glassmeyer, EPA, the largest assessment of PFAS in drinking water, EPA's Third Unregulated Contaminant Rule (UCMR 3), developed baseline data on six chemicals in nearly 5,000 water systems, although Schaider noted that UCMR 3 could have missed detections of PFAS around current state health standards based on the detection limits of those methods. Glassmeyer stated other smaller studies have analyzed PFAS in source water, treated drinking water, and tap water, and DoD is testing drinking water consumed on military bases. Available data have provided estimates of the relative contribution of drinking water to overall PFOA and PFOS exposure, with less information for other PFAS.

Active Research: Glassmeyer noted UCMR 5, currently under review for sampling between 2023 and 2025, is expected to require certain public water systems to monitor for all PFAS with validated analytical methods (currently 29 substances). The new methods (537.1 and 533) provide lower detection limits (around 1-2 ng/L) than prior UCMR.[8] USGS is sampling domestic and public supply wells nationwide for PFAS, and an EPA portal will compile and share PFAS state and federal monitoring data. In addition, ATSDR is developing assessments to determine relative contribution of drinking water to body burden for other chemicals beyond PFOS and PFOA.

Research Gaps and Discussion: Glassmeyer identified three broad areas for study: (1) which PFAS are present in drinking water, (2) sources of the PFAS that enter drinking water, and (3) importance of drinking water contribution to overall PFAS

[8] For more information, see https://www.epa.gov/pfas/epa-pfas-drinking-water-laboratory-methods.

exposure. Related to the first area, she said questions remain about whether and how to increase the number of PFAS monitored. New methods are being developed, but Andrew Gillespie, EPA, cautioned they need to be documented, tested, validated, and made public to be useful. Andrew Lindstrom, EPA, stressed the need to identify the chemicals in AFFF-impacted drinking water, which is the "most prevalent, highest-exposure scenario." Better understanding of whether PFAS precursors are transformed into stable PFAS during treatment of drinking water is also needed, Glassmeyer added. Matthew Waterbury, DoD, commented while analysis with validated methods for specific compounds is important, risk communication in conveying the findings to consumers is also critical.

Related to sources of PFAS in drinking water, Schaider suggested that chemical fingerprints, based on the relative abundances of a wide range of different PFAS, could be used to identify the source of contamination. Breysse pointed out the need first to develop relevant fingerprints. Focazio stated that USGS is designing a vulnerability mapping project to mine data on potential sources and target monitoring efforts. Breysse commented that states that are more aggressive in searching for contaminated sites have found them, which points to the fact that there is much to learn. Private wells are typically unmonitored, another gap that may need attention, suggested Glassmeyer.

Related to the role of drinking water in overall PFAS exposure, Glassmeyer pointed to the need to better understand not only ingestion, but also dermal and inhalation routes of exposure, as well as the contribution of water relative to other pathways such as food and dust.

Diet

State of the Science: Validated analytical methods are available for 16 types of PFAS in different foods, generally below 100 parts per trillion, reported Paul South, FDA. Two collections of Total Diet Study samples representing the average U.S. diet (94 foods in total) have been analyzed for PFAS, as have other targeted foods, such as beef muscle. Few detections were found: two in tilapia and one in ground turkey. Most foods grown or produced in areas without PFAS contamination do not have detectable levels of the chemicals; in contrast, PFAS in food has been detected when water with elevated levels of PFAS is used for irrigation or animal operations. Susan Genualdi, FDA, explained that detection limits are currently 20 to 100 parts per trillion, depending on the food and analyte. "We feel confident that we are measuring food at a concentration that wouldn't be a concern in the human diet at this point," she said.

FDA's authorization process for food contact applications concluded that potential PFAS exposure from current applications is low, according to South. Paul Honigfort, FDA, elaborated that the process requires manufacturers to provide FDA with information on exposure using "100 percent migration assumptions [from the application to the food] based on a worst-case scenario."

Active Research: South described FDA and USDA efforts to expand the analytical methods used and foods studied. Work is underway to improve analytical methods to include additional PFAS and extend to other food matrices, increase testing capacity, and develop rapid test methods. The agencies are working with NIST to develop standard reference materials for PFAS in human and animal foods, as there are few reference materials for PFAS. The agencies are also working with states to understand the uptake of PFAS into human and animal food from PFAS-containing biosolids or AFFF contamination.

Research Gaps and Discussion: A primary discussion point centered on conflicting findings about PFAS levels in food. Schaider and planning committee member Thomas Webster, Boston University, referred to European Food Safety Authority conclusions that diet is the main source of exposure for the general population and to other studies showing associations between PFAS serum levels and certain foods, such as fish and shellfish. In explaining the few detects found in U.S. food samples, South noted the Total Diet Study is limited to the most commonly eaten foods nationwide, and FDA currently has PFAS results from two out of the six U.S. regions sampled. Additional sampling and analysis is planned. To expand the research, he said, "We're going to be using targeted sampling to look specifically at certain commodities that have in the past shown to have higher levels of PFAS, and perhaps contribute more to PFAS exposure in the population." South stated data are needed on different products, including more processed foods, as well as more targeted sampling of foods shown to have higher levels of PFAS and food grown in areas with known PFAS contamination. More predictive information about PFAS presence and accumulation could be used to target resources, such as by location or species. Lindstrom noted the need for characterizations of lactational exposures that are focused on more compounds.

Kappes highlighted the need to understand background levels of PFAS in agricultural water sources and livestock feed, as well as better tools for PFAS extraction and detection in animal tissues. Schaider commented that, as with drinking water, expanded analytical methods for more PFAS are needed. Toxicological reference values to assess PFAS levels in foods are an additional gap, noted South.

Occupational Exposures

State of the Science: PFAS exposure occurs in many occupational settings, said Beth Whelan, NIOSH, with firefighting and some manufacturing the most well-known. A study in Nordic countries found high PFAS levels in ski wax technicians. Use in occupational settings has likely changed over the past two decades, and there are probably worker groups with elevated PFAS levels that remain unstudied, she added. Unlike in environmental settings or with the general public, occupational exposure typically is through inhalation or dermal exposure. Most studies of dermal PFAS exposure have focused on PFOA, although other PFAS can also penetrate skin.

Active Research: NIOSH and NTP are conducting a feasibility study of 150 workers across industries, measuring PFAS in serum and air samples and looking at certain measures of health. Much current research focuses on firefighters, including the Firefighter Cancer Cohort Study,[9] which will look at serum PFAS in airport and wildland firefighters in addition to air samples collected during training exercises using AFFF. Another set of studies concentrates on exposure from firefighter textiles. As of October 2020, DoD offers blood sampling for PFAS to its approximately 20,000 firefighters during annual medical examinations.

Research Gaps and Discussion: Whelan identified the need for occupational reference limits and guidance and the need to learn about occupational exposures beyond those already known. Understanding the potential hazards of replacement compounds for legacy PFAS and developing methods for quantifying occupational exposures are further areas for research. The contributions of different exposure routes are not well understood, she added. Miriam Calkins, NIOSH, singled out the relatively little information on dermal exposure. The pharmacokinetics of less-studied PFAS in the human body are not well understood, which Whelan noted has relevance for timing of sample collection. Wireman suggested that trend analysis based on the DoD Serum Repository (available with samples since 1990) may provide information on longer-term exposures and contribute to health studies.

Other Pathways

State of the Science: Elaine Cohen Hubal, EPA, noted the presence of PFAS in national biomonitoring suggests exposures beyond drinking water may be important. Other pathways of exposure for PFAS include diet (discussed above), dust, and consumer products. House dust measurements suggest widespread presence of PFAS in residential environments. Other potential pathways include outdoor air, soil, indoor surfaces, and some workplaces. Existing studies have mainly focused on PFOS and PFOA, with limited information on other chemicals.

Active Research: Literature reviews are compiling what is known about other exposure pathways. EPA is developing methods for measuring air emissions from production and manufacturing facilities. Additionally, paired research efforts are taking advantage of existing samples and data from other studies, including the American Healthy Home Study, National Children's Study, and ATSDR's Multi-Site Health Study. This work aims to combine serum measurements, drinking water monitoring, and data on other exposure pathways, such as dust samples.

Research Gaps and Discussion: Cohen Hubal reiterated the need to better understand contributions of PFAS exposure from sources other than water and diet, with a focus on emerging chemicals and on inhalation and dermal exposure pathways. Gillespie underscored the lack of knowledge on dermal absorption and urged more definitive experimentation. Lindstrom also noted a lack of data on airborne exposures near incinerator facilities. Cohen Hubal called for concordant biomonitoring and environmental measurements studies, sharing a concern expressed by Schaider that few such studies have been done. She also noted limited studies to evaluate inhalation of volatile precursors as an exposure pathway.

> *"If we focus on the most prevalent highest exposure scenario—the AFFF-impacted drinking water scenario—there's a great need to understand the complete universe of compounds that are present in AFFF formulations. There are tens, hundreds, maybe even thousands of compounds there." – Andrew Lindstrom, EPA*

Understanding Predominant Exposure Sources

State of the Science: To tie the presentations together, Andrew Lindstrom summarized predominant exposure sources, noting contaminated drinking water is the most likely source among subpopulations with the highest blood levels, often caused by AFFF or releases from nearby industrial sources. Diet has been considered an important, low-level exposure source in the general population, although testing of the general U.S. food supply has detected few PFAS, a finding that differs from studies in other countries. Fish and seafood typically represent a large part of the dietary exposure but food packaging also appears to play a role. Lactational exposures affect nursing infants. Additional sources within homes, schools, and workplaces include consumer products and dust. He stressed almost all published studies are limited to no more than 18 PFAS compounds.

Active Research: Lindstrom referred to several studies previously mentioned to understand exposure sources. EPA also has ongoing characterization studies examining emissions from PFAS production, use, and disposal facilities.

Research Gaps and Discussion: Lindstrom highlighted additional research and data needs, including total exposure studies that pair biomonitoring with simultaneous data on PFAS in drinking water, food, air, and products to tease out the contribution from each. He noted that different parts of the country, age, socioeconomic status, and other variables need to be considered, given the heterogeneity and exposure-specific nature of PFAS exposures. Echoing a previously discussed gap, Lindstrom stressed the need for improved methods for and application of nontargeted and total organofluorine analyses across different media, such as food, drinking water, soil, and dust. An improved understanding of dermal absorption and inhalation exposures across a broader suite of compounds is also needed, he said.

When asked about the highest priority research gap, Lindstrom said, in his view, a priority is understanding AFFF-contaminated drinking water exposures based on the number of people affected, the many compounds present, and biomonitoring evidence to date. Kent Thomas, EPA, added that significant questions remain about factors that affect exposures. For example, a firefighter who is a regular blood donor is likely to have lower PFAS levels in their system than one

[9] See https://www.ffccs.org.

who is not. Gillespie highlighted the importance of understanding the effects of contaminated water on the food supply, such as through irrigated agriculture. Calkins stressed the "major gap in the literature" related to occupational exposures.

Planning committee members also weighed in. Webster suggested the need to better understand exposure from PFAS in food. Kannan emphasized the importance of understanding the role that PFAS precursors may play in exposure. Schaider noted the difficulties in assessing PFAS exposure when monitoring is limited to relatively few chemicals. Kannan suggested combining nontargeted analysis and total organofluorine methods to help identify what traditional measurements are missing; Lindstrom agreed both are needed but should be applied judiciously to inform each other. Finally, Schaider and Alan Ducatman, West Virginia University, suggested the challenges in identifying which PFAS to look for in different sources could be overcome through more collaboration between chemical manufacturers and scientists, a comment that Ducatman noted was made by many of the workshop's public attendees.

EXPERIMENTAL TOXICOLOGY STUDIES

In the second technical session, participants discussed PFAS toxicology, including in vivo studies; pharmacokinetics; in vitro, high-throughput and mechanistic screening; and adverse outcome pathways and other frameworks for evidence integration of PFAS toxicity.

In Vivo Studies

State of the Science: The current body of in vivo knowledge is mostly based on rodent studies, primarily mice, and focuses on long- and short-chained sulfonates and carboxylates, Chad Blystone, NIEHS, explained. Endpoints of note include cancer, organ toxicity, immunomodulation, and first generation (F1) reproductive/developmental effects. The toxicokinetics vary by species, chemical and, in some cases, sex of the animal model, although limited data are available for emerging PFAS. Despite the limitations, Blystone and Katie O'Shaughnessy, EPA, noted vivo research can be useful in understanding complex, multifactorial disease outcomes by identifying potential mechanisms of action and their relevance to human health outcomes.

> *"There are virtually no in vivo data for some of the more commonly detected PFAS that are included in the standard analytical methods—as just two examples, perfluoropentanoic acid, C5, and perfluoroheptanoic acid, C7, that are often found in drinking water."*
> *– Gloria Post, New Jersey Department of Environmental Protection and planning committee member*

Active Research: Blystone said ongoing research aims to better understand the health effects associated with PFAS exposure and determine the relevant mechanisms of action involved in adverse health outcomes. EPA is planning a developmental toxicity study using perfluoro-2-methoxyacetic acid (PFMOAA). They are also conducting transcriptomic and cell biology-based mechanistic research to study how PFAS affects rat neurodevelopment. NIEHS is conducting transcriptomics, kinetic, and mechanistic research for several PFAS, including PFOA, GenX, and AFFF formulations. NIEHS studies on emergent PFAS evaluate liver, metabolic, neurobehavioral, and immunological endpoints.

Research Gaps and Discussion: Gaps include limited information on mechanisms of action, dose-response relationships, and PFAS mixtures. Penelope Rice, FDA, and Michael DeVito and Justin Conley, both from EPA, highlighted the limited information on dose-response relationships for PFAS and the need to interpret animal dosimetry data for human exposure scenarios. Blystone also emphasized the limited understanding of newer PFAS and how legacy and emerging PFAS interact and affect toxicity.

Animal models can provide valuable information in many areas of PFAS research, such as vaccine response, lactation deficits, and liver enzyme upregulation, but participants noted limitations in this approach. Differences in directionality of cholesterol and triglyceride changes between animals and humans show better models may be needed to study these effects, said Sue Fenton, NIEHS/NTP. She noted other important considerations may include diet (whether the animal is fed a controlled lab diet or more typical human diet) and differences in respiration (particularly for studies on inhalation effects.).

Pharmacokinetics

State of the Science: As presented by Michael DeVito, PFAS with chains of more than six carbons have half-lives that can last from months to years in humans. Long half-lives are related to such mechanisms as lack of metabolism, renal uptake, and protein binding in the serum and liver. Although there are physiologically based pharmacokinetic (PBPK) models for PFOA and PFOS, data for emerging PFAS are limited. Rice stated that for perfluorinated acids, the dose affects the toxicokinetics, with higher doses resulting in faster elimination of the chemical. DeVito suggested using in vitro data to group PFAS into bins according to their short, medium, and long half-lives instead of assuming chain length automatically correlates with half-life.

Active Research: DeVito shared that EPA, in collaboration with NTP, is building pharmacokinetic models and generating data for a PFAS screening library. This work will help researchers better understand the range of PFAS structures and their associated biological and pharmacokinetic activity. ATSDR is also gathering data on PFAS pharmacokinetics to inform potential class-based approaches to studying PFAS. Additionally, ATSDR is developing a public interface where community members can use PFAS water concentrations to estimate their serum PFAS levels.

Research Gaps and Discussion: DeVito underscored the need for additional pharmacokinetic modeling for most PFAS in rodents, zebrafish, and humans. Human data on half-lives, hepatic clearance, metabolic susceptibility, renal absorption, and the effect of population variability on these factors are lacking. Pharmacokinetic data for replacement PFAS are especially important, as those chemicals make up the majority of PFAS.

In Vitro, High-Throughput, and Mechanistic Studies

State of the Science: Rusty Thomas, EPA, explained in vitro and mechanistic data are available only for a small number of PFAS. The mechanisms at play following PFAS exposure may include nuclear pathways, stress response pathways, and effects on cellular lipid membranes, but the exact mechanism for a certain PFAS likely depends on chain length and functional group. Rice added that different PFAS metabolites may activate different mechanisms of action. DeVito noted as more in vitro data are collected, they can be used to develop human and high-throughput studies to ensure that study methodologies accurately represent the mechanisms of PFAS exposure and human health impacts.

Active Research: Rusty Thomas highlighted current research on using targeted in vitro testing and data to facilitate approaches to grouping PFAS. Research is being conducted to generate mechanistic data for ~120 structurally diverse PFAS to help group PFAS into categories for read-across, potentially allowing data on well-studied PFAS to inform toxicity assessment of less-studied chemicals. Grace Patlewicz, EPA, highlighted ongoing work to develop and apply in silico approaches to predict PFAS transformation pathways.

Research Gaps and Discussion: Multiple discussants emphasized the need for new in vitro methods and assays. Rusty Thomas identified limitations in some in vitro methods (e.g., simulating appropriate metabolic activity within the assay). He stressed the need to better understand interactions between co-occurring PFAS and cross-species concordance of mechanistic and adverse health effect data. Lisa Sweeney, DoD, suggested developing more in vitro methods for legacy and less-studied PFAS, validated by in vivo studies. Understanding data for individual PFAS and interactions between PFAS is especially important because, as Blystone and planning committee member Gloria Post, New Jersey Department of Environmental Protection, commented, read-across between different PFAS may not yield accurate information, especially for PFAS with different toxicokinetic properties.

A recurring discussion point was whether in vitro assays provide accurate data on metabolized PFAS. According to Rice, in vitro studies that use PFAS parent compounds may not be accurate if, in humans or animals, the target cells from those studies would actually be exposed to a metabolite rather than the parent compound. She and Rusty Thomas stated that metabolized PFAS could have different toxicokinetic properties in the assays, thereby skewing interpretation of PFAS biological activity.

Adverse Outcome Pathways and Other Frameworks to Integrate Evidence

State of the Science: Given the range of testing and data collection methods as well as the thousands of existing PFAS, data integration is crucial in understanding PFAS toxicokinetics and associated health effects, according to several participants. Michelle Angrish, EPA, explained that evidence integration allows researchers to transparently conduct causal analysis, design research questions, and determine data gaps. Currently, there is a systematic evidence map for about 150 PFAS and plans to use data integration frameworks to prioritize research on less-studied PFAS. Adverse outcome pathways (AOPs) piece together key chemical exposure-induced biological effects from molecular and cellular level effects along plausible pathways to inform causality or adverse outcomes.[10] They are used to document a web of events and information on PFAS to view them as a cohesive whole.

Active Research: Angrish described EPA's focus is to combine mechanistic and biological effects data to develop a better understanding of PFAS. This could allow for data extrapolation between species and the integration of ecotoxicity data with data relevant to human health, she added. EPA is expanding its systematic evidence map to cover about 430 PFAS, which can be used to inform test methodology.

Research Gaps and Discussion: Gaps discussed by Angrish include major data integration issues that limit understanding of PFAS pathways and modes of action, evaluation of the accuracy of evidence integration predictions, and application of frameworks to multifactorial human health outcomes. These data are necessary points of integration that allow for standardization between studies and more effective weight of evidence evaluations. DeVito noted existing PFAS groupings are becoming more established, but the range of solubility, stability, and volatility of PFAS, as well as limited data on emerging PFAS, limit the accuracy and efficacy of data integration and quantitative structure-activity relationship (QSAR) models.

HUMAN HEALTH OUTCOMES

As backdrop to the consideration of human health, David Savitz provided an overview of PFAS epidemiology and identified challenges in determining human health effects from PFAS. In the past 10–15 years, he explained, PFAS epidemiology work has primarily focused on a relatively small number of contaminated community drinking water supplies, which provide a large population to study with substantial exposure. Major studies on PFAS and human health outcomes include the C8

[10] See https://www.nap.edu/catalog/24635/using-21st-century-science-to-improve-risk-related-evaluations.

Health Study from West Virginia, cohort studies from Ronneby, Sweden and Veneto, Italy, and the ongoing ATSDR Multi-Site Health Study. In these locations, contaminated drinking water affected people across a range of socioeconomic conditions, reducing confounding factors. However, even these populations are often not large enough to determine causation for rare health outcomes, such as cancers. The different sites studied may have different combinations of chemicals in the water supply, which complicates comparisons across sites. Savitz noted that few studies exist on populations with substantial, well-documented gradients in exposures.

Following Savitz's presentation, federal researchers provided overviews of research and data gaps and discussed associations between PFAS and immunological effects; metabolic, hepatic, and other non-cancer effects; cancer effects; and reproductive, perinatal, and developmental effects.

Immunological Effects

State of the Science: Bonnie Joubert, NIEHS, summarized research showing that exposure to several types of PFAS decreased antibody responses to some vaccines in adults and children. Webster noted vaccine response was the critical endpoint used by the European Food Safety Authority in its PFAS assessment. However, Savitz cautioned against overinterpretation of antibody measurements given his view that data linking decreased antibody response and increased incidence of clinical infection are lacking.

The relationships between PFAS exposure and other immunological effects have also been studied, but the results have been mixed. The C8 Health Project found an association between PFOA and ulcerative colitis, but Savitz said results need to be replicated in additional studies. Joubert noted a potential association between PFOA and asthma and between PFAS exposure and increased incidence of infectious disease, although data are limited. Mark Johnson, DoD, highlighted the complexity of the associations between PFAS and immunological endpoints by pointing out that PFAS may potentially cause both immunosuppression, such as reduced antibody production, and hypersensitivity, such as asthma and ulcerative colitis. The complexity of the immune system may have implications for the level of PFAS exposure needed to induce a health impact.

Active Research: Ongoing studies, including NIEHS longitudinal epidemiology studies, NIOSH occupational exposure studies, and the ATSDR Multi-Site Health Study, look at links between PFAS exposure and immunological response, Joubert said. She also described work to examine the impact of PFAS to COVID-19 susceptibility and illness in healthcare providers and first responders. ATSDR is planning a prospective study on possible associations between exposure and susceptibility to viral infection, including COVID-19.

Research Gaps and Discussion: The discussion centered on how to improve and correctly interpret data on immunological effects. Joubert focused on the need for better understanding of the mechanisms of immunotoxicity and how changes in immune function lead to health effects. Additionally, she pointed out that the long-term impacts of observed immunological effects are unknown. Without more data on the persistence of immunological effects, it is difficult to determine future health risks associated with exposure.

Metabolic, Hepatic, and Other Non-Cancer Effects

State of the Science: According to Marian Pavuk, ATSDR, an increase in total and low-density lipoprotein (LDL) cholesterol is the strongest indicator of a metabolic effect of PFAS, although he noted increased cholesterol does not necessarily lead to development of cardiovascular disease. Webster observed serum lipids are among the better-studied outcomes from an epidemiologic perspective. However, Ducatman pointed out that the increased use of lipid-lowering medications may limit researchers' ability to study whether and how PFAS effects upon cholesterol and lipid handling may relate to cardiovascular disease outcomes.

Other health effects have been associated with PFAS exposure, but with mixed results. In terms of hepatic effects, Pavuk reported associations between PFAS exposure and elevated liver enzymes, as well as non-alcoholic fatty liver disease. Kimberly Gray, NIEHS, described some associations between childhood PFAS exposure and lower bone mineral density. Neurological and thyroid effects have also been studied, she said, and associations were found between PFAS exposure and behavioral problems in children, as well as between PFAS exposure and increased hormone levels in adult females. However, these associations are less established given the complexity of these organ systems and the difficulty in measuring health effects.

Active Research: From a methodological perspective, Pavuk called attention to research on the window of susceptibility as well as the importance of collecting PFAS exposure data from ongoing studies. Researchers are tapping into existing clinical trials, such as those related to diabetes, to efficiently gather more data on PFAS exposure and health outcomes. Additionally, the ATSDR Multi-Site Health Study will evaluate potential associations between PFAS exposure and many health effects, including thyroid and kidney function, osteoporosis/osteoarthritis, and neurological outcomes.

Research Gaps and Discussion: Data gaps include improving exposure measures, developing a better understanding of co-exposures, and determining how innovative studies such as intervention-based approaches may provide more complete information on health outcomes, as raised by Pavuk and several other discussants. Pavuk explained that exposure estimations based on drinking water modeling or other indirect measures are not as accurate as direct exposure measures. He stressed understanding mixtures is key to accurately measure exposure and associate it with an effect. Gray highlighted the need for an understanding of potential interactions between PFAS and other environmental exposures, as well as more information on complex health effects and the role that subclinical changes changes, such as thyroid hormones, may play in determining

multifactorial health outcomes. Joubert suggested that intervention studies can be conducted and the results compared to observational epidemiology studies to form a complete picture of multifactorial outcomes such as metabolic effects.

Cancer

> *"... the gap we have in front of us is a mechanism of action. ...And when we understand the mechanism, I think we're going to have a better handle on how animal models can be used to mirror the human condition, and what cancers we will expect to see in humans who are exposed to certain levels of PFAS."*
> *– James Smith, NMCPHC, DoD*

State of the Science: In high-exposure settings, the evidence for associations between PFAS exposure and cancer risk is strongest for PFOA and kidney and testicular cancers, according to Jonathan Hofmann, National Cancer Institute (NCI). He noted the International Agency for Research on Cancer classified PFOA as a "possible human carcinogen" based in part on observed increased risks of kidney and testicular cancer in humans. Mark Purdue, NCI, clarified that existing studies on testicular cancer have included a relatively small number of cases. Hofmann added that studies have found some associations with other cancer types; for example, lower-level exposures to some PFAS, including PFOS, have been associated with prostate and breast cancers, although evidence for these associations is less consistent than that for PFOA and kidney and testicular cancers.

Active Research: Hofmann reported that a recent study within the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial observed an increased risk of kidney cancer among individuals with elevated serum PFOA concentrations. NCI plans to continue this work to determine whether these findings are replicable in other populations. They will also study associations between PFAS exposure and testicular and other cancers using nested studies within PLCO, the Finnish Maternity Cohort, and the DoD Serum Repository.

Research Gaps and Discussion: Hofmann highlighted the need to determine the biologic plausibility and mechanisms of action through which PFAS may influence cancer development, including for emerging and replacement PFAS. He also distinguished between data from heavily exposed populations and the general population, stating it remains unclear whether PFAS exposure at levels observed in the general population increases cancer risk. Purdue posited that comparing PFAS-associated cancer development data across multiple cancer histologic and molecular characteristics could help researchers identify plausible mechanisms. Hofmann, Purdue, and Andrea Winquist, NCEH, agreed with Savitz that small study population sizes in many cancer studies of highly exposed populations limit researchers' ability to effectively study these outcomes, citing kidney, testicular, and pediatric cancers respectively.

Reproductive, Perinatal, and Developmental Effects

State of the Science: The most discussed reproductive and developmental health effects in this panel were fetal growth, reproduction, and neurodevelopment. PFAS crosses the placenta and the blood-brain barrier, said Frank Bove, ATSDR, and can be transferred from mother to child via breastfeeding. Bove and Fenton reported associations between PFAS exposure and low birthweight and fetal growth restriction. However, Fenton and planning committee member Scott Bartell, University of California, Irvine, suggested that confounding by maternal physiology may affect these associations, with Fenton urging researchers to consider potential associations between preeclampsia and lower birthweight when interpreting data. Bove also mentioned associations between PFAS exposure and decreased sperm count and motility.

Neurodevelopment studies have yielded mixed results. Bove reviewed a potential association between PFAS exposure and development of ADHD and discussed evidence of effect modification due to sex, maternal parity, and socioeconomic status. Earlier, Gray had noted an association between PFAS exposure and behavioral difficulties but that no effect on cognition was observed.

Active Research: Bove described ongoing studies regarding potential effects of PFAS on reproductive effects from fertilization to birth weight, performance of children on neurobehavioral tests, health of women following pregnancy, and endometriosis. Longitudinal studies will include measures of cognition, behavior, and intelligence. NHANES data will continue to be used to evaluate reproductive and developmental outcomes when possible.

Research Gaps and Discussion: The discussion of data gaps for reproductive and developmental outcomes included critical exposure windows, sex-specific differences in outcomes, and more data on understudied reproductive and developmental effects. Bove highlighted the importance of determining exposure susceptibility for certain windows of exposure. Although exposures later in the pregnancy may appear to increase the risk of low birth weight, measuring exposures late in pregnancy could potentially result in confounding due to hemodynamics. Further study is needed to determine whether and to what degree confounding might affect the relationship between PFAS exposure, exposure timing, and low birth weight. He also highlighted the need for studies on PFAS mixture toxicity. Acknowledging sex-specific differences in health outcomes, he suggested further study of sex-related effect modification.

Presenters and discussants noted additional data would be informative for certain endpoints. Fenton suggested additional thyroid measurements to determine whether multiple health effects are likely due to endocrine disruption. Bove noted that birth defects and miscarriages have not been well-studied and that more sufficiently powered studies are needed on associations between PFAS exposure and fetal growth restriction and weight gain in children. Gray recommended neurological studies that include more severe outcomes such as neuropsychiatric effects. Joubert suggested more standardized protocols to integrate data from longitudinal studies with measures from multiple time points.

CROSS-CUTTING ISSUES IN PFAS RISK ASSESSMENT

In the final technical session, the presenters and discussants covered cross-cutting issues in risk assessment, including handling mixtures, class-based approaches, and emerging issues.

Handling Mixtures

> *"When we are evaluating mixtures, it is important that we consider how much of [the exposure is from] a particular source. ...Basically, the better characterization of exposure, the better the problem definition for...toxicity assessment [of mixtures]."*
> *– Moiz Mumtaz, ATSDR*

State of the Science: Because assessments of a single chemical may underestimate risk, mixture risk assessment methods are needed, said Moiz Mumtaz, ATSDR. The ATSDR Mixtures Framework[11] provides three assessment approaches: whole mixture, similar mixture, and a components-based hazard index (HI). Because the toxicology database for PFAS mixtures risk assessment is less robust than desired, the capacity of mixture risk assessment is currently limited to whole mixture analysis, according to James Smith.

Active Research: Mumtaz highlighted research to fill gaps in the toxicology data. For example, in vivo studies are looking at dose additivity in defined mixtures for specific endpoints. In vitro studies include screening-level tools to assess mixture toxicity, and novel statistical tools are being developed because it is impossible to experimentally test all possible combinations and mixtures.

Research Gaps and Discussion: Mumtaz highlighted the underlying gaps in exposure, toxicity, toxicokinetics, and health effects data, discussed previously, that need to be addressed to evaluate the combined toxicity of PFAS. Biological modeling is also needed to determine thresholds for interactions and to estimate relative potency. In his earlier presentation, Savitz called for strategies to understand health effects in epidemiology studies when multiple forms of PFAS are involved. Mumtaz highlighted the need for a systems approach with respect to mixtures, rather than prioritizing specific endpoints.

Sunderland suggested looking at specific exposure vectors and conducting in vitro testing of typical combinations of PFAS to understand their health effects. For example, she noted, seafood contains a specific chemical signature of long-chain PFAS, which are the more bioaccumulative compounds, and this signature is also detected in people. Bartell asked if the toxic equivalency factor (TEF) used for other chemical classes could apply to PFAS. Smith said he does not think there is enough information about the thousands of PFAS compounds to group them by mechanisms of action. Conley said a TEF-type approach would require being able to scale different compounds using relative potencies based on an adverse effect, but multiple receptors are activated across various PFAS, with different effects across different life stages. Mumtaz added such an approach would require dose-response data across a large number of different PFAS to group chemicals with congruent dose-response curves.

Class-based Approaches to Risk Assessment

> *"I think, it's fair to say that there are [currently] insufficient toxicological as well as toxicokinetic data to group the PFAS that are currently in commercial use and in the environment on a robust mechanistic basis. ...There are limited intrinsic property, exposure, and effects data to inform selection among the various class-based approaches that are being proposed."*
> *– Rusty Thomas, EPA*

State of the Science: According to Rusty Thomas, class-based approaches are needed, and such approaches have been proposed based on structure (i.e., chain length and functional groups), health effects, and intrinsic properties such as bioaccumulation or mobility. However, he noted, "we're really at a data-poor and data-starved state to help inform these categories and groups." Thomas explained that PFAS substances thus present unique challenges for grouping into classes for risk assessment. Dorman noted for other classes of compounds, in vitro and computational approaches sometimes do not predict outcome data from toxicology or epidemiology studies well.

Active Research: Rusty Thomas said research is underway to improve understanding of the mechanistic and toxicokinetic properties of a broader range of PFAS, which will inform grouping and identify additional testing needs. Work is ongoing to identify chemicals in PFAS mixtures and create objective, reproducible PFAS groups that are structurally and mechanistically consistent, and available data on physicochemical properties and bioaccumulation are being culled from the literature to update existing models.

Research Gaps and Discussion: Rusty Thomas stated that more data on exposure, intrinsic properties, toxicology, toxicokinetics, and health effects are needed to group PFAS and select among different class-based approaches. Mechanistic properties of volatile and semi-volatile PFAS remain poorly understood. Sunderland observed the lack of basic chemical-physical data for the tremendous number of new compounds and PFAS-containing materials being produced. Thomas also emphasized the need for data-rich analogs ("anchor chemicals") in many, if not all, PFAS groups.

Emerging Issues

Sunderland introduced a general discussion of emerging issues related to risk assessment. Post urged a quicker approach to advance in vivo studies on newly identified PFAS to support states as they develop risk assessments and guidance values.

[11] See https://www.atsdr.cdc.gov/interactionprofiles/ipga.html.

Conley noted novel PFAS are sometimes not commercially available in a purified standard form to support in vivo testing, although Barry Marcel, DoD, added that a database is now available listing 430 commercially available PFAS.

Schaider asked about improving analytical capabilities and standards development for emerging PFAS, noting nontargeted analysis lacks the capacity to provide quantitative information. Breysse agreed analytical standards are crucial, but new, targeted analytical methods take a long time to develop. Gillespie said some companies share laboratory-grade standards once a chemical has been detected in the environment. Post noted the lack of public data on chemical production, use, and discharge, particularly for PFAS with limited physical, chemical, or toxicity data, requires spending federal resources to determine information that may already exist. Place said the nontargeted analysis community is working to develop semi-quantitative methods for nontargeted analyses. Gillespie noted EPA is also working on other methods to quantify emerging PFAS, including total organofluorine analysis, combustion ion chromatography, and particle-induced gamma-ray emission, and is building a website with information on these research-grade methods.

CLOSING REMARKS

In the last session, the planning committee shared a series of slides that distilled what they took away as key points from each presentation. These distillations are reflected in the text above. Dorman concluded the workshop by recognizing the challenge in summarizing a tremendous body of research into very short sessions and thanked the federal researchers, planning committee, and National Academies staff for their participation.

DISCLAIMER: This Proceedings of a Workshop—in Brief has been prepared by **Stephanie Johnson**, **Kaley Beins**, and **Paula Whitacre** with assistance from **Elizabeth Boyle** as a factual summary of what occurred at the meeting. The committee's role was limited to planning the event. The statements made are those of the individual workshop participants and do not necessarily represent the views of all participants, the planning committee, the Board on Environmental Studies and Toxicology, or the National Academies.

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