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Risk assessment of per- and polyfluoroalkyl substances (PFAS) in food: Symposium proceedings

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ABSTRACT

Per- and polyfluoroalkyl substances (PFAS) comprise a large group of synthetic chemicals with a long history of use in industrial and consumer products. Regulatory and public health agencies have recognized that exposure to high levels of some PFAS may cause adverse health effects including reduced antibody responses to vaccines, increased cholesterol levels, low infant birth weight, and increased risk of high blood pressure. Although considerable effort has been devoted to the study of PFAS in the environment, there are significant gaps in our understanding of the potential human exposure to PFAS from food and food packaging. In 2020, a two-session symposium titled Identifying Science Gaps for Risk Assessment of Per- and Polyfluoroalkyl Substances (PFAS) in Food was held by ILSI North America (in 2021, ILSI North America has evolved to become the Institute for the Advancement of Food and Nutrition Sciences [IAFNS]). Recognizing the importance of measurement systems in PFAS risk assessment, the first session focused on analytical methods and science gaps for detecting and quantifying PFAS in various foods and packaging materials. The second session addressed exposure routes into foods, including an overview of the United States Department of Agriculture Food Safety Inspection Service work on PFAS and recent toxicological studies by the Food and Drug Administration on biopersistence and potential human effects of short-chain PFAS used as replacement for longer-chain biopersistent PFAS. Expert presentations encompassed US regulatory, academic, industry, and non-profit perspectives and were followed by panel discussions.

1. Introduction and purpose

The safety of food and food packaging materials from unintentional contamination has gained significant attention for health, environmental, and regulatory concerns. Much of this attention has been focused on per- and polyfluoroalkyl substances (PFAS) used for oil and moisture resistance in packaging. A two-session virtual symposium on risk assessment of PFAS in food was held in 2020 that aimed to address current and emerging consumer exposure and health concerns of PFAS in food and food packaging. This symposium was hosted by ILSI North America. In 2021, ILSI North America evolved to become the Institute for the Advancement of Food and Nutrition Sciences (IAFNS). The symposium also aimed to identify knowledge gaps in risk assessment of PFAS in food that could be addressed by the Institute's collaborative research model.

The symposium was attended virtually by approximately 200 scientists, engineers, and regulatory professionals from public, private, and academic institutions. These proceedings summarize the key concepts of the presentations. They are not intended to offer a comprehensive summary of information shared during the workshop. The views summarized reflect the content of symposium presentations made by the speakers and should not be construed as consensus among symposium participants or the public-sector and private-sector members of ILSI North America. Symposium presentation recordings are publicly available at www.iafns.org/our-work/food-safety/packaging/

2. Screening and quantification of workflows for PFAS in food packaging

Speaker: Keith Vorst, PhD. Iowa State University, Polymer and Food Protection Consortium.

PFAS are globally used in a variety of consumer goods due to their unique functional properties. There are many routes of potential exposure to PFAS from non-stick cookware, grease-resistant paper, fast food wrappers, microwave popcorn bags, and retail and convenience packaging. Long-chain PFAS were voluntarily discontinued by manufacturers in the USA and are not intentionally added to food packaging, consistent with FDA guidelines. Short-chain PFAS and fluorinated acrylate polymers remain authorized for use in packaging and industrial applications. A comprehensive, rapid, and cost-effective quantification of all 4000+ PFAS compounds is not currently practical given today's technology, methods, and workflows. Recent publications and work by the author's laboratory have established methods for detection of total fluorine as an indicator of PFAS. Variability in screening and quantification for PFAS such as sample preparation and residual concentrations in cellulose-based products can have a significant impact on reported values to assess consumer exposure in food packaging.

Given the potential health and migration concerns associated with PFAS in food contact materials (FCM), it is imperative that analytical methods be developed to accurately and efficiently quantify various PFAS in a variety of matrices. Method sensitivity for detection of PFAS has been improved dramatically in the last few decades by the use of advanced analytical technologies such as liquid chromatography-

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tandem mass spectrometry (LC-MS/MS), triple quadrupole tandem mass spectrometry coupled to liquid chromatography (LC-(QqQ)MS/MS) and liquid chromatography quadrupole time-of-flight tandem mass spectrometry (LC-QTOF). However, efforts to improve extraction and clean-up of solid-matrix samples for subsequent analysis on those technologies are still needed in order to minimize uncertainties and assure instrumental reproducibility and accuracy in workflows across global laboratories. Several extraction methods have been reported for the extraction of PFAS in different matrices (Nakayama et al., 2019). Examples of methods used on solid matrices include the following: solid-liquid extraction (SLE) (Sinclair et al., 2007), pressurized liquid extraction (PLE) (Poothong et al., 2012; Zafeiraki et al., 2014), ultrasound assisted extraction (UAE) (García-Valcárcel & Tadeo, 2013), microwave assisted extraction (MAE) (Beser et al., 2011), and focused ultrasound solid-liquid extraction (FUSLE) (Martínez-Moral & Tena, 2013; Monge Brenes et al., 2019; Zabaletata et al., 2014). Among all these methods, FUSLE has been validated and shown to be a low-cost, fast, simple and safe extraction technique with PFAS recoveries on food matrices and popcorn bags of nearly 100% (Moreta, C., & Tena, M. T., 2013; 2014). Although it is known that a reduction in particle size could always lead to increased extraction efficiency, none of these studies address this variable, which seem to pose a challenge whenever sampling solid matrices. The goal of this presentation is to investigate the effect of two particle size reduction techniques, ball milling and cutting grinding, on the PFAS recovery of three types of spiked food contact materials (microwave popcorn bags, molded fiber bowl, and wrappers) using focused ultrasound solid-liquid extraction (FUSLE) technique for extraction of the targeted fluorinated compounds.

Previous work by the author found increasing perfluorocarbon length reduced concentration needed for functional performance (Curtzwiler et al., 2021). Paper packaging found shorter chain chemistries (C4) to provide functional differences in higher concentrations (1200 + ppm) compared to long chain (C10) at 38 ppm. This study provides a starting point to understand and differentiate products containing intentionally added fluorochemistry versus incidental environmental contamination such as processing waste, composting, or end-of-life concerns from landfills or nuisance liter. Further preliminary work by our team identified the effect of particle size differences in recovery based on sample preparation method. Different milling techniques (ball mill, coupon cutting, and blade mill) were evaluated on sample popcorn bags, molded fiber bowls, and paper food wrappers spiked with 16 per and polyfluoroalkyl (PFAS) compounds. Preliminary results found that the ball mill allowed for better recovery of spiked PFAS compounds, with coupon cutting having the lowest recovery with greatest variability (data not shown). Volatility of short chains, after being extracted, was an issue. Great care must be taken during sample preparation as time, temperature, and sonication all affect the recovery of PFAS compound. Future research and method validation are needed to develop standard methods for sample preparation, extraction and recovery methods for screening and quantification of PFAS compounds.

For additional information, see references (Curtzwiler et al., 2021; Monge Brenes et al., 2019, pp. 1–10).

3. Method development and investigation into perfluoroalkyl and polyfluoroalkyl substances (PFAS) in the US food supply

Speaker: Susan Genualdi, PhD, Research Chemist, FDA, Center of Food Safety and Applied Nutrition.

The dietary exposure to PFAS substances through foods consumed in the US has not been well characterized (see Fig. 1). Potential sources of PFAS contamination of foods in the human diet include contaminated water affecting agricultural products, livestock, and seafood, and migration from food contact materials. The FDA's Total Diet Study (TDS) routinely collects and monitors composite samples of table-ready highly consumed foods each year. Samples collected through this program in 2018 were used to develop a Quick, Easy, Cheap, Effective, Rugged, Safe (QuEChERS) extraction method for PFAS with analysis by liquid chromatography mass spectrometry. A total of 16 PFAS were analyzed in a variety of commodities including fruits, vegetables, milk, cheese, grains, meats, and seafood. This method was used to analyze 179 TDS composite food samples collected in different regions of the country and representing foods available in those regions. This work builds on previous methods for the evaluation of cranberries, milk, and shell-fish (Genualdi et al., 2017; Young et al., 2012, 2013) for detection of perfluorochemicals using liquid chromatography-tandem mass spectrometry. Results of these studies highlight needed adjustments to decrease the method detection limit (MDL) in total dissolved solid samples. Current work utilized the previously published cranberry method (Fig. 2) and investigated adding a nitrogen concentration step to include 5 mL of filtered QuEChERS extract and concentration to 0.5 mL. The inclusion of a nitrogen concentration step resulted in lower MDLs for most produce samples and milk, but the increase in matrix caused rapid column deterioration for other complex samples such as meat, breads, and other dairy. Switching the instrument used for analysis from a 6500 (cranberry work) to a 6500 plus resulted in detection limits orders of magnitude lower negating the need for nitrogen concentration of TDS samples.

During method development, challenges arose with matrix suppression, interferences, false positives, and method blanks. Investigations were also made into improving chromatography and additional clean-up steps. Early eluting matrix components resulted in false positives and are especially problematic for compounds with only one transition. The development of this method will allow the FDA to continue monitoring PFAS compounds in the US food supply. This method is single lab validated for the extraction of PFAS in produce, dairy, meat and bread samples, and future work is needed for a multi-lab validation.

For additional information, see reference (Genualdi et al., 2017) and www.fda.gov/media/131510/download.

4. Challenges associated with the analysis of PFAS in food and food contact materials

Speaker: Charles Neslund, Scientific Officer, Eurofins Lancaster Laboratory Environmental.

PFAS are considered persistent organic pollutants (POPs). As such, there is an expectation that they remain in the environment for years. As the analysis and investigation of sites contaminated with PFAS and the impact to drinking water continues to mature, there is a growing interest in the contribution of PFAS from ingestion of foods to overall human exposure. To date, the only commonly acceptable methodology for the analysis of PFAS was a drinking water method, EPA 537.1, which covers a somewhat limited list of PFAS. In December 2019, the EPA published Method 533, which has a broader list of compounds and uses a different extraction chemistry but is still designed for drinking water. Eurofins commonly receives requests for PFAS analysis in vegetables grown in fields treated with biosolids and milk from dairies where cows ingested PFAS contaminated water or grazed on contaminated pastures, as well as food contact materials (FCM). This presentation discussed the challenges and experiences of PFAS testing from the perspective of a commercial laboratory with a focus on development of in-house laboratory techniques and recently published approaches by the FDA.

The current EPA Method 537.1 (Shoemaker & Tettenhorst, 2018) for potable water allows for 14 PFAS compounds +4 replacement compounds (GenX, Adona, F53b (major and minor)) for a total of 18 compounds to be analyzed with a styrene divinylbenzene solid phase extraction cartridge using an internal standard quantification. This method has limitations with solid matrices requiring sample preparation and "clean-up," and was intended for drinking water with low total soluble solids (TSS) and low total dissolved solids (TDS). The new and current EPA Method 533 (Rosenblum & Wendelken, 2019) utilizes solid

	Spike Recovery (%)					
	Molded Fiber Bowl		Brown Sandwich Bag		Microwave Popcorn Bag	
Analyte	Ball Analytical Mill	Blade Analytical Mill	Ball Analytical Mill	Blade Analytical Mill	Ball Analytical Mill	Blade Analytical Mill
PFBA	91.3	85.6	86.5	127.7	-112.3*	418.0*
PFPeA	88.5	86.4	72.4	74.9	100.7	198.3*
L-PFBS	68.9	67.2	67.2	84.5	96.0	77.4
PFHxA	128.7	129.9	76.2	40.5	637.5*	1749.9*
L-PFPeS	74.4	71.3	66.9	74.1	91.0	72.4
HPFO-DA (GenX)	72.3	40.1	65.0	56.6	87.9	71.0
PFHpA	96.9	95.0	71.1	71.6	99.4	115.2
L-PFHxS	84.0	74.1	83.5	83.8	102.0	89.9
NaDONA	88.9	88.6	72.4	73.3	80.7	68.4
L-PFHpS	84.0	76.7	73.1	61.2	93.8	86.4
PFOA	93.3	86.3	75.9	64.9	76.5	67.6
PFOS	84.4	76.6	58.3	50.0	112.7	101.6
PFNA	95.9	83.7	65.7	52.5	96.9	76.2
9Cl-PF3ONS	79.6	85.6	72.5	59.9	123.1	105.1
PFDA	82.6	80.3	80.7	60.2	109.1	109.7
11Cl-PF3OUdS	86.9	94.1	110.2	112.1	133.3	126.2

*Copious amount of these substances were found in these samples. Spike level chosen (20 ng/g sample) was below level needed for accurate recovery.

Fig. 1. Spike recovery of PFAS compounds using ball mill, and blade mill.

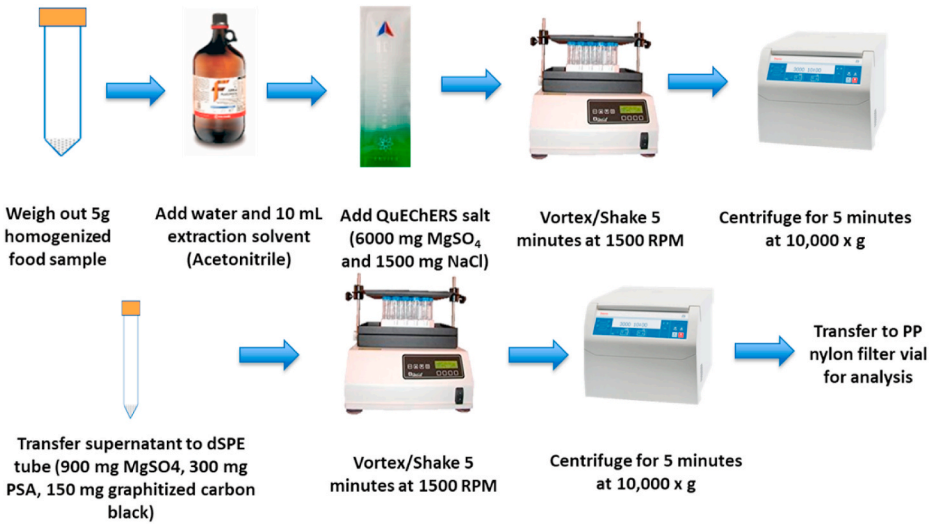

Fig. 2. Method development for TDS samples.

phase extraction (SPE) with weak anion exchange (WAX) designed to accommodate short chain acids. This method employs an isotope dilution for recovery correction of analyte concentrations with many of the same compounds as EPA Method 537.1 but includes a total 25 compounds. Method 533 is intended to include groundwater and surface water but still does not apply to solid matrices and does not include sample preparation and clean-up required for solid samples such as packaging. The lab, therefore, developed its current method for PFAS using quantification by isotope dilution and has been applied to multiple matrices, including but not limited to, drinking water and non-potable water, solid samples such as packaging, soil, landfill leachate, and sludge. This method is used to quantify 36 compounds (25 isotopically labeled extracted internal standards) and utilizes SPE with weak anion exchange. This method has seen widespread adoption due a high degree of quantitation accuracy and precision, broadest list of compounds, and widest range of matrices. This method can be used in support of total oxidizable precursor assay (TOP) and yields the lowest reporting limits across all matrices.

The challenge with method selection for analysis of PFAS in food is the absence of validated methods. Recent progress has been made in method development and more clarity given to the utilization of approaches for various food types such as vegetables, fruits, dairy, meat/fish, and eggs (Bizkarguenaga et al., 2016; Genualdi et al., 2017; Li et al., 2015; Liu et al., 2017; Moreta & Tena, 2014; Trudel et al., 2008; Young et al., 2013; Zabaletata et al., 2014; Zhang et al., 2015). Some key elements to the approach selected include the use of an isotope dilution, weak anion exchange chemistry, sorbent/binding agent to "normalize" matrix, inclusion of additional clean-up, and the use of at least two

transitions masses per compound where possible. To provide rapid screening of samples for potential PFAS compounds, additional methods have been developed to evaluate precursors or total fluorine content. These methods, such as the TOP assay and total organic fluorine, may not provide exact quantification or identification of specific PFAS compounds that result in the "total PFAS" content, but do provide screening to determine likelihood of fluorine chemistry and thus PFAS (Zhang et al., 2019). Newer techniques for non-targeted analysis such as Liquid Chromatography/Mass Spectroscopy-quadrapole time of flight spectrometry (LC/MS-qTOF) provide accurate mass detection to determine peaks of known/unknown identity. The mass determination would rely on regression of accurate mass determination for possible identification. This method shows promise for a more expansive screen of total potential PFAS content with fewer sample preparations and quantification procedures. Further research is needed for the global adoption of consensus standards, description of processes, and evidence on how such processes can foster the implementation of official methods of analysis.

For additional information, see reference (Neslund, 2020).

5. Developing international consensus performance standards and official methods of analysis for PFAS: Benefits and challenges

Speaker: Palmer Orlandi, PhD, Chief Science Officer, Association of Official Analytical Collaboration (AOAC).

PFAS compounds are recognized as persistent, bioaccumulative, and potentially toxic contaminants present in the environment. Their ubiquity presents a significant concern to human health. Whereas most of the surveillance and testing thus far for PFAS has focused on soil, sediment, and water using validated and uniformly accepted methodologies, their pervasive presence in the environment and their use in food contact paper and packaging has created a need to expand testing capabilities to foods and other food-related matrices. Currently, a single-laboratory validated method developed by the US FDA in 2019 is the only method in use to compile exposure data on PFAS in foods. Though limited in scope (16 PFAS), this method has laid the groundwork for future method (matrix and analyte) extension.

There are still many knowledge gaps on risks associated with PFAS (e.g., prevalence, exposure, and disparate regulatory trends worldwide). All such future activities to address these gaps, however, will need to be supported through analytical testing by the adoption of international performance standards and the development of official compendial methods.

PFAS compounds provide a unique analytical challenge. They are readily absorbed into soil and sediment through surface and ground water leaching and subsequently taken up into agricultural crops. It is imperative that trusted test methods be developed to detect all significant PFAS analogs and to perform in a wide range of matrices to ensure accuracy in biosurveillance activities, the compilation of human exposure data, and to meet regulatory requirements. Food packaging must also be a focus as it represents a potential source for PFAS exposure through their inclusion as water and grease repellant coatings.

Analytical challenges, such as those presented by PFAS, are routinely addressed by AOAC INTERNATIONAL, a globally recognized non-profit standards development organization (SDO). As an impartial, third-party, science-based convener, AOAC gathers stakeholder communities and subject matter experts to jointly define and agree upon those standard method performance requirements (SMPRs) needed to drive the development and adoption of consensus compendial methods under a set of operating principles to balance all interests of the stakeholders while providing transparency, openness, lack of dominance, due process, consensus, and an appeals process. Resulting SMPRs document the need for a method and provide a detailed description of how the method must perform (e.g., a fit-for-purpose statement, limit of detection and quantification values, breadth of applicability, etc.). An overview of AOAC's process is illustrated in Fig. 3. All resulting methods are then evaluated for adoption based on their performance against the SMPRs and on established validation criteria as validation data documents precision and reproducibility across multiple laboratories.

The value of consensus-based processes for developing method performance standards and adoption of official methods of analysis—particularly those employed by AOAC INTERNATIONAL—are well documented throughout the global scientific, regulatory, and public health communities. Extending this process to the analytical challenges presented by PFAS will uniformly provide trust in data-generating activities and through that trust, help the global community to better understand the breadth of PFAS' environmental effects, to help mitigate PFAS exposures, and diminish its impact on consumer and environmental health.

6. Dietary pathways and routes of human exposure to PFAS

Speakers: William Frez, PhD, and Dana McCue, MPH, EHS Support, Inc.

PFAS are a manmade class of environmentally-persistent organofluorine chemicals widely used across various industries over the past 70 years. Toxicological evidence suggests that exposure to certain PFAS compounds, particularly long-chain varieties, can pose human health risks to the immune, endocrine, and reproductive systems. In this presentation, we review a conceptual PFAS exposure model that describes sources, transport processes, and exposure pathways to human receptors.

In terms of sources, major sources of human PFAS exposure can be broken down into two categories: point sources and non-point sources. Primary point sources are associated with industrial activities, such as fire training/response sites. Non-point sources, which are the focus of this presentation, potentially include food packaging, food products, and drinking water. Transport processes depend on the chemical nature of the PFAS and can range from migration to ground water, run-off to surface water, and long-range atmospheric deposition, which all can

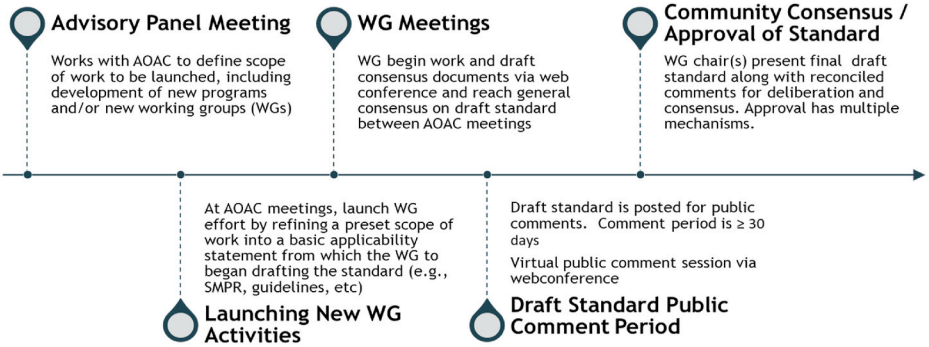

Fig. 3. A concept placed into practice: AOAC consensus development framework.

potentially lead to contamination of agricultural products and, ultimately, exposure to humans. Potential human exposure pathways for PFAS include inhalation, incidental soil and dust ingestion, dermal contact, diet, and drinking water. European data suggest that, next to point-source contamination, drinking water is the single most important source of human exposure to PFAS. However, studies are needed to understand the relative contribution of various PFAS sources to human dietary exposure in the US.

Elucidating food exposure pathways is a work in progress. At a high level, the two primary routes of PFAS into food are bioaccumulation at the source and exposure via processing and packaging (Fig. 4). Bioaccumulation-related pathways typically reflect long-term uses of PFAS and can include biosolids, which refer to industrial sludges and ashes containing nutrients that can enhance soils and agricultural production. PFAS present in biosolids can leach into ground water potentially leading to drinking water contamination (Lindstrom et al., 2011). They can also be absorbed by agricultural crops leading to dietary exposure (Blaine et al., 2014).

PFAS, especially short-chain PFAS, can accumulate in the edible portions of crops when grown in PFAS-contaminated soil or water. In comparison to the accumulation of short-chain PFAS in crops, accumulation potential in fish and beef is high for certain long-chain PFAS, particularly PFOS (Lupton et al., 2015; Stahl et al., 2014). Also, in contrast to other persistent chemicals, PFAS tend to partition to proteins rather than lipids where they have been observed in liver, kidney, and muscle tissue (Jones et al., 2003). Processing and packaging exposure pathways reflect current production and use of PFAS. PFAS in water- and grease-resistant packaging, such as fast-food wrappers, can leach into food and increase dietary exposure. PFAS currently used in food packaging are mainly short-chain varieties and fluorotelomer-based derivatives. Based on measurements of total fluorine as a PFAS surrogate, PFAS have been detected in a variety of food wrappers and paperboard (Schaider et al., 2017). The high water-solubility of PFAS has contributed to their presence in various water sources in the vicinity of high-probability point sources, such as manufacturing and fire-fighting sites. Our understanding of PFAS water contamination has greatly expanded from statewide and nationwide surveys between 1999 and 2017. Results of these surveys indicate that some drinking water concentrations of PFAS exceed the EPA's current 2016 health advisory limit of 70 ng/L for PFOA and PFOS individually or combined, potentially exposing approximately 6 million Americans (Sunderland et al., 2019).

A review of food supply data collected in the European Union indicates the presence of PFAS across various food categories, particularly meat and fish, with higher concentrations in fish. However, there were comparatively fewer PFAS detections in studies conducted by the FDA on the US food supply. The assessment of PFAS in the US food supply is limited as compared to the European Union. Nonetheless, based on the best available science to-date, there is no indication that PFAS in food present a human health concern. Overall, the health risk posed through dietary exposures remains to be fully defined.

The sparsity of data in the US has not allowed for risk assessment and development of food standards or acceptable food safety levels; current regulatory inroads have been though food packaging and drinking water. The FDA has banned PFOA and PFOS in food packaging and recently in July 2020 announced a phase out of 6:2 FTOH. In addition, several states have adopted or proposed bills that ban or limit PFAS in food packaging. At the federal and state levels, there has been a focus on regulating drinking water. As noted earlier, in 2016 the EPA established a lifetime health advisory level of 70 ng/L for PFOA and PFOS. There are currently no enforceable Maximum Contaminant Levels (MCL) for PFAS. However, the EPA has initiated the process to propose a regulatory MCL for PFAS under the Safe Drinking Water Act. State regulatory bodies have been more proactive in setting regulatory PFAS limits. However, the general lack of consensus on toxicological data, receptor population and corresponding exposure assumptions has led to widely variable standards among states.

The path forward for understanding risks posed by PFAS in food includes filling data gaps related to dietary exposure, movement of PFAS through the food supply, and establishing safe levels for those exposed to this group of chemicals. Government efforts to address these gaps include expanded PFAS testing of USDA regulated foods, expanded testing of PFAS in FDA's TDS, and state-level testing of certain foods such as dairy products.

7. Recent developments related to PFAS: analytical approaches, surveillance testing, and incident response

Speaker: Alexander Domesle, JD, MS, Food Safety and Inspection Service, U.S. Department of Agriculture.

As part of the National Residue Program, the USDA Food Safety and Inspection Service (FSIS) samples meat, poultry, and egg products and tests them for a wide range of veterinary drugs, pesticides, and contaminants. This ensures that the food supply does not contain unsafe chemical residues and also supports the regulatory efforts of our partner agencies such as the FDA and the EPA. Over the past decade, FSIS has engaged with government partners to respond to situations where food-producing animals are exposed to PFAS substances. Routes of exposure include agricultural irrigation water used for feed crops, as well as live animals potentially contaminated with PFAS from industrial or commercial sources. PFAS in the water may also contaminate biosludge that is collected at wastewater treatment plants and spread over agricultural fields.

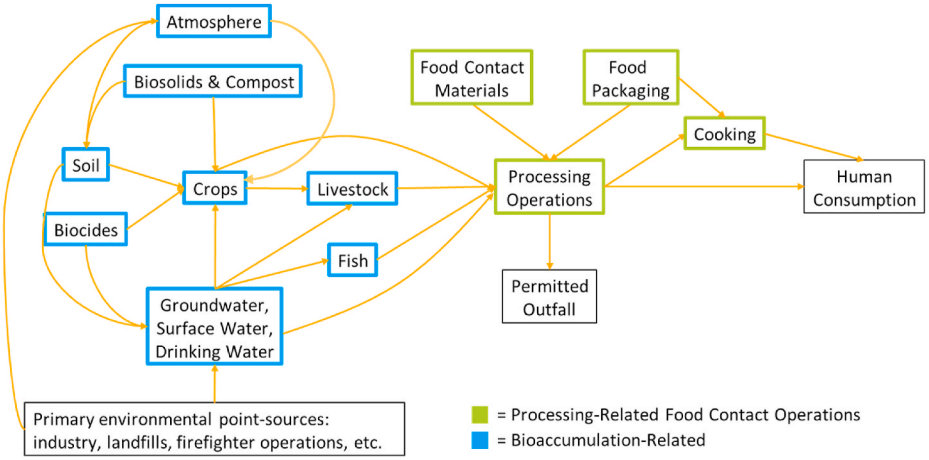

Fig. 4. Potential pathways for PFAS entry into the US food supply.

The USDA, through FSIS, has been addressing the potential for PFAS presence in USDA-regulated products in three main ways: a) developing analytical methods for detecting PFAS in food products through FSIS laboratories; b) using analytical methods to initiate exploratory testing of commercial samples of meat and poultry as part of the National Residue Program surveillance; c) supporting producers and state governments dealing with PFAS contamination at specific locations. The USDA is working closely with Federal partners such as FDA, EPA, and others, to meet these objectives.

The agency uses a laboratory system comprising three laboratories spread across the country (Georgia, Missouri, and California) that includes quality assurance and emergency response staff. Tissue samples from slaughter, processing, and import establishments across the country are sent daily to these laboratories to conduct a full suite of tests for a variety of hazards that include pathological conditions, microbial pathogens and indicator organisms, chemical residues of pesticides and veterinary drugs, and chemical contaminants such as metals and PFAS. These regulatory laboratories do not do research per se but do their own method development to attend a high throughput of tests. In the fiscal year of 2019, more than 100,000 samples were analyzed, more than 525,000 tests were performed, and more than 2.65 million results were reported.

In the past two years, FSIS has developed and validated a method for detecting16 per- and polyfluoroalkyl substances (PFAS) in USDA-regulated meat and poultry products. The method has been validated in bovine muscle and plasma samples and is currently being evaluated for use in porcine, poultry, and Siluriformes (catfish) muscle. This rapid and cost-effective method has been validated for PFAS compounds of various carbon-chain lengths (4-C to 18-C), which include perfluorosulfonic acids as well as perfluorocarboxylic acids. These methods are publicly available as part of the FSIS Chemistry Laboratory Guidebook (CLG) through the agency's website:

https://www.fsis.usda.gov/wps/portal/fsis/topics/science/laboratories-and-procedures/guidebooks-and-methods/chemistry-laboratory-guidebook.

The surveillance testing conducted by FSIS is done under the National Residue Program. This program provides a structured process for identifying, evaluating, and responding to chemical compounds of concern in food animals. FSIS works closely with other regulatory agencies to design a program that not only protects public health, but also will signal if there is any widespread misuse of those types of chemicals, or whether the assessments underlining the approval for those chemicals need to be updated.

Current PFAS testing at FSIS is exploratory in nature, with primary focus on data collection in support of potential agency action going forward (there are no current quantitative regulatory levels for PFAS in meat and poultry). However, detection of these products at levels of concern would lead to an accelerated action towards a regulatory response to ensue product safety.

In FY 2020, the USDA tested more than 1100 bovine muscle samples for PFAS. These samples, representing dairy cows, beef cows, and steers, were from animals that had been condemned by USDA in-plant inspectors for unrelated reasons. Of the 1100 samples tested, only 4 samples showed positive results for PFOS, and all were at levels below 1 ppb. Moreover, no other PFAS were detected in these samples. The next step for PFAS testing under the National Residue Program is to continue the bovine testing for at least another fiscal year. The USDA is also planning to add other animal protein sources for testing such as swine, chicken, and Siluriformes with the objective of understanding the potential presence of PFAS in USDA regulated food supply. As these data are being collected or monitored in real time, potential actions that need to be taken will be drawn from internal discussions with FSIS partners.

The USDA, along with the FDA and other partners, consults with states and producers and offers testing resources. Among those interactions, the most significant in the past decade involved a large dairy in the Southwestern US where 4000 to 5000 animals were supplied with PFOS-contaminated drinking water. The supplied water came from an aquifer that was potentially contaminated from fire-fighting foam from a nearby air force base. The USDA worked closely with the FDA, the state government, the EPA, and the dairy owner to help resolve the issue. Resulting actions included preventing the milk from entering commerce and prohibiting the animals from going to slaughter pending further testing and analysis. In 2019, the aforementioned protocol for PFAS testing was specifically developed to test these animals. In cooperation with the USDA Agriculture Service (ARS), which purchased several animals from the farm, various types of samples were acquired for testing including muscle samples, organs, skin, milk, blood, urine, and feces. Some animals were kept alive and a mitigation proposal took effect to move these animals from exposure to another area where the water would be considered PFOS free. A depletion curve is being established through monitoring PFOS plasma levels of these animals before potentially clearing them for slaughter. These data are still being generated and analyzed. An interim screening level for PFOS in beef, to assist contextualize testing results, has been developed in partnership with the FDA. The outcome of this work is to apply context to these test results, and ultimately develop a mitigation strategy to evaluate the PFOS level depletion in these animals. By July 2020, two assessments (four months apart) for PFOS levels in blood plasma samples were made from animals that had been removed from the exposure area. PFOS levels in the second assessment were the same or higher than the first raising questions about a potential second PFAS source and rate of PFAS depletion in tissues.

8. Characterizing biopersistence potential of the metabolite 5:3 fluorotelomer carboxylic ACID after repeated oral exposure to the 6:2 fluorotelomer alcohol

Speaker: Shruti V. Kabadi, PhD, Pharmacologist (Toxicology Team Lead), Office of Food Additive Safety, Center for Food Safety and Applied Nutrition, US FDA.

This presentation addressed the toxicokinetic (TK) evaluation of 6:2 Fluorotelomer alcohol (6:2 FTOH), which is a PFAS chemical with a six-carbon chain length where the carbons are fully fluorinated (C6-PFAS). 6:2 FTOH is a monomeric constituent and impurity found in polymeric food contact substances. This presentation provided a description of recent TK evaluations of 6:2 FTOH performed over the past few years using classical TK modelling of experimental data in rats.

6:2 FTOH is used as a grease-proofing agent in food contact materials such as microwave popcorn bags, fast food containers and wrappers, and pizza boxes. Genetic toxicity studies on 6:2 FTOH indicated no concern for genetic toxicity. Other studies reviewed for 6:2 FTOH included systemic toxicity data such as a 90-day oral toxicity studies in rats, single generation productive toxicity studies in rats and mice, teratology studies in rats, and OECD 422 screen (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test) in rats. Additionally, available TK data for 6:2 FTOH indicated that it is rapidly metabolized to form perfluorinated carboxylic acids (PFCAs) such as perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), and 5:3 fluorotelomer carboxylic acid (5:3 acid).

Available TK data (at the time) on 6:2 FTOH were reviewed and discussed in a publication by Kabadi et al. (2018). This presentation began with a metabolic scheme of 6:2 FTOH (Fig. 5). The figure showed that 6:2 FTOH metabolizes into several PFCAs. Of those, PFHpA, 5:3 Acid, and PFHxA were the focus of analysis since the concentrations for the other metabolites were generally below the level of detection (LOD).

Notably, a study by Russell et al. (2015) summarized TK datasets on 6:2 FTOH, specifically a single-exposure inhalation study on male and female rats and a repeated exposure study of a PFAS mixture, including 6:2 FTOH conducted in an occupational setting on humans. FDA performed an internal exposure-based assessment of these data using non-compartment TK modeling (Kabadi et al., 2018). Internal exposure was calculated in the terms of TK estimates of area under the curve (AUC),

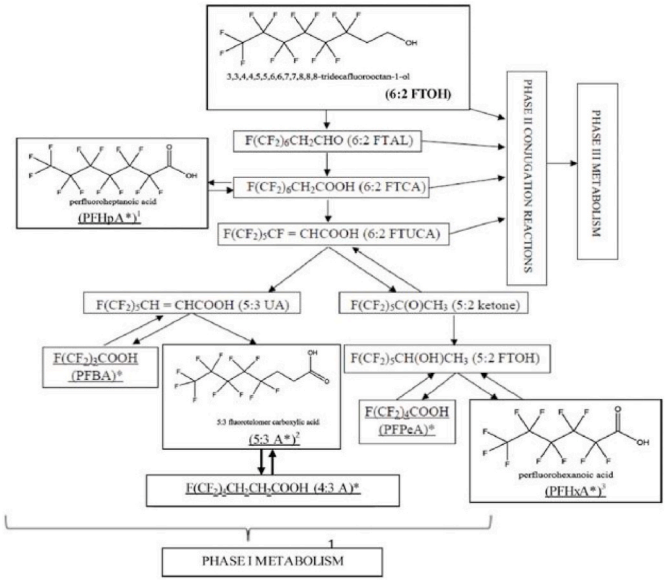

Fig. 5. Proposed scheme for 6:2 FTOH metabolism. Chemicals marked with (*) are metabolites whose TK parameters were estimated (Kabadi et al., 2018).

elimination rate constant (kel) and clearance. Key findings of the assessment were that internal exposure to 5:3 acid is highest in both rats and humans indicating that it is a potential metabolite of concern and that the scaled human clearance of 5:3 acid decreased with increasing exposure to the parent compound. This was an interesting finding since, generally, the clearance of a substance does not change at increasing doses. This indicated that the elimination process could potentially follow non-linear TK. This analysis also concluded that additional TK data from repeated exposure studies are required to fully characterize the biopersistence potential of 5:3 acid after repeated oral exposure to 6:2 FTOH.

More recently, a 90-day repeated oral exposure 6:2 FTOH TK study conducted on male and female rats at different doses was reviewed. In this study, 6:2 FTOH and some metabolites, including 5:3 acid, PFHxA and PFHpA, were sampled from plasma, liver, and fat at different time points. The main conclusion from the review of this study was that 5:3 acid was the only metabolite that was consistently reported in plasma, fat and liver at all recovery time points, while levels of the other metabolites were generally below the LOD. Moreover, the data were of adequate quality for performing a TK analysis to estimate TK parameters (Kabadi et al., 2020). Using one compartment TK modeling, certain TK parameters were estimated, including elimination half-life ($t_{1/2}$) and time to steady state (t_{ss}). The conclusions of this TK assessment were: 1) 5:3 acid had t_{ss} of approx. one year in plasma, liver, and fat of male and female rats, 2) most of the longest t_{ss} values for 5:3 acid in plasma, liver and fat were observed at the lowest dose tested (5 mg/kg bw/d), and 3) although no significant differences were identified in the $t_{1/2}$ and t_{ss} of 5:3 acid in the plasma and evaluated tissues between sexes, mean plasma and tissue 5:3 acid concentrations were significantly higher in females than males. The underlying mechanisms of these TK effects are yet to be investigated. In conclusion, this analysis reported the first characterization of biopersistence potential of 5:3 acid based on steady state TK parameters after repeated oral exposure to the parent compound 6:2 FTOH using experimental data in rats.

9. Comparative analysis of the potential human health effects of 6:2 fluorotelomer alcohol versus perfluorohexanoic acid

Speaker: Penelope Rice, PhD, Toxicologist, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition, US FDA.

C6-PFAS are compounds containing as a moiety that is a straight alkyl chain containing six fully fluorinated carbon atoms. Examples are C6-PFAS acrylate and methacrylate monomers, and polymers made from these monomers, as well as PFHxA where the sixth carbon is part of the carboxylic group and 6:2 FTOH. PFHxA and 6:2 FTOH are impurities in the C6-PFAS polymeric coatings used in food packaging, textiles, and floor waxes. 6:2 FTOH is also a metabolic byproduct of other impurities in C6-PFAS polymers.

The C6-PFAS compounds are used as replacements for long-chain PFAS (LC-PFAS) which have been shown to be highly persistent in animal tissue and the environment and have been linked to immunotoxicity, reproductive and developmental toxicity, and carcinogenicity. At the time of authorization, C6-PFAS had not been shown to be biopersistent, and thus, were not considered to be as toxicologically concerning as LC-PFAS. Recent studies, including the work of Kabadi et al. presented at this symposium, have raised concerns regarding the biopersistence of the 5:3 acid metabolite of 6:2 FTOH (Kabadi et al., 2018) (Russell et al., 2015). The 5:3 acid metabolite is a polyfluorinated compound that apparently is not broken down or is broken down very slowly, raising questions about the similarity of the toxicological effects of 6:2 FTOH and PFHxA.

This presentation presents newly available information to the toxicological profile of 6:2 FTOH to directly compare the toxicological profiles of PFHxA and 6:2 FTOH. To determine whether data for PFHxA could adequately describe potential human health effects of 6:2 FTOH exposure, qualitative toxicological data from identical studies conducted in the same species on both compounds were assessed. This work is not a quantitative risk assessment.

Results of the toxicokinetic (TK) comparison of PFHxA and 6:2 FTOH indicate that both are well absorbed; however, PFHxA is not metabolized whereas the 6:2 FTOH is extensively metabolized into several stable compounds. Distribution is very similar, except PFHxA accumulates in plasma, liver, and kidney whereas 6:2 FTOH accumulates in plasma, liver, and fat. The major route of excretion in PFHxA is urine, but 6:2 FTOH can also be excreted in feces dependent upon metabolite. For PFHxA, the half-lives of male and female rats are extremely short and measured in hours, whereas the 5:3 acid is measured in days. The 5:3 acid is as biopersistent in rats as PFOS and more biopersistent than PFOA in rats.

Side-by-side comparisons of apical effects come from standard repeated-dose oral studies in adult rodents (see Table 1). Similarities of apical effects of PFHxA and 6:2 FTOH include hepatocellular hypertrophy and increased liver weight. In contrast, there is a marked increase in adverse liver effects with 6:2 FTOH including hepatocellular necrosis inflammation, oval cell hyperplasia, and biliary hyperplasia in addition to cytoproliferative lesions in mice.

In summary, liver effects with 6:2 FTOH are more adverse and indicate proliferation, whereas with PFHxA there is only hypertrophy. The kidney is comparatively spared with PFHxA, whereas 6:2 FTOH effects include increased kidney weights, renal tubular necrosis, basophilia, dilation, mineralization, and degeneration. In these studies, 6:2 FTOH renal effects are often the cause of early mortality, particularly in females. Apical effects on the immune system are similar, as expected because both 5:3 acid and PFHxA are peroxisome proliferators, which can lead to immunosuppression. Apical effects of 6:2 FTOH on the thyroid were not consistent, but with PFHxA there were occasional increased weights and follicular cell hypertrophy likely secondary to enzyme induction in the liver as has been seen with other compounds that are liver enzyme inducers. Points of departure in repeated dose oral studies include that the 6:2 FTOH data has generally lower NOAELs and LOAELs than for PFHxA indicating that the 6:2 FTOH is more toxic than PFHxA when assessed under similar study designs.

Comparisons of apical effects on reproduction and development come from studies on both rats and mice. There were marked differences between PFHxA and 6:2 FTOH in apical effects on reproduction, with 6:2 FTOH in rats leading to decreased numbers of dams delivering litters and decreased gestation index, possibly secondary to high dam mortality,

Table 1
Apical effects of PFHxA and 6:2 FTOH on rodent liver and kidney from repeated-dose oral studies.

Compound	Absorption	Metabolism	Distribution	Excretion	t1/2 male rats (approximate)	t1/2 female rats (approximate)
PFHxA	Well-absorbed	Not metabolized	Plasma, liver and kidney	Urine (major) and feces (to a small extent)	2.2–2.8 h	2.3–2.6 h
6:2 FTOH	Well-absorbed	Extensively metabolized. Stable metabolites: PFHxA, 5:3 acid, 4:3 acid, PFPeA, PFBA, PFHpA.	Plasma, liver and fat	Urine and/or feces, depending on metabolite	5:3 acid: plasma: 64.2 d (5 mg/kg) 59.6 d (25mg/kg) liver: 78.7 d (5 mg/kg) 61.3 d (25 mg/kg) fat: 99 d (5 mg/kg) 55.4 d (25 mg/kg)	5:3 acid: plasma: 66.6 d (5 mg/kg) 59.2 d (25 mg/kg) liver: 91.2 d (5 mg/kg) 59.2 d (25 mg/kg) fat: 70 d (5 mg/kg) 43.68 d (25 mg/kg)

and 6:2 FTOH in mice leading to decreased maternal feed consumption, body weight gain during lactation, mammary gland lesions, decreased uterine and ovarian weights, and increased numbers of anestrus. There were also increased adverse development effects with the 6:2 FTOH compared to the PFHxA. Both compounds led to decreased body weight, however, with 6:2 FTOH in rats there was also increased skull ossification delays, rib abnormalities, and pup mortality, and in mice there was decreased pup survival and bodyweight during lactation. Points of departure from these studies indicate increased potency with the 6:2 FTOH versus PFHxA in rats and mice.

Two conclusions can be drawn from this analysis. First, the toxicological dataset for PFHxA is not appropriate to assess the hazards associated with 6:2 FTOH exposure. This conclusion is based on quantitative and qualitative differences in effects on liver and kidneys between rats administered 6:2 FTOH versus rats administered PFHxA/NaPFHx. This conclusion is also based on the biopersistence of 5:3 acid versus rapid elimination of PFHxA. The second conclusion is that the toxicological profile of 6:2 FTOH indicates that it is significantly more toxic than PFHxA. Thus, the use of toxicological studies conducted on PFHxA for risk assessment of 6:2 FTOH may underestimate the human health risk associated with a given daily 6:2 FTOH exposure and fail to capture all apical effects.

For more information, see Kabadi et al. (2019), Kabadi et al. (2020) and Rice et al. (2020).

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