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Dietary Exposure to PFAS: Gut Toxicity as a Gateway to Systemic Health Effects

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ABSTRACT

Per- and polyfluoroalkyl substances (PFAS), known as "forever chemicals," are persistent global contaminants that infiltrate the agricultural food chain (e.g., concentrations of 0.159 ng/g have been measured in leafy vegetables such as lettuce), as shown by Piva et al. (2023). By extension, these chemicals pose a significant threat to human health. This review synthesizes current evidence to identify the pathway from environmental PFAS contamination to adverse health outcomes with a specific focus on the gastrointestinal tract as the critical gateway for dietary exposure. It examines how PFAS enter the environment, via industrial discharge, biosolids, and atmospheric deposition, and are taken up by crops, with uptake varying by PFAS type and crop. In one study, the mean total PFAS concentration in ready-to-eat leafy vegetable produces reached 0.13 ng/g (SD 0.09), compared with 0.07 ng/g (SD 0.07) for fresh vegetables and 0.06 ng/g (SD 0.05) for frozen vegetables, indicating clear variability in PFAS levels by processing category (Piva et al., 2023). Upon ingestion, PFAS disrupt the gut barrier and microbiome, promoting a state of chronic inflammation. This gut-level pathology is mechanistically linked to systemic effects, including immunosuppression, endocrine disruption, and metabolic disease. This review further highlights distinct exposure vulnerabilities, with rural populations often facing higher risks from point sources and urban populations being exposed to complex mixtures from commercial foods and packaging. Finally, we identify critical knowledge gaps, such as the need for long-term studies on chronic exposure and a better understanding of PFAS mixture toxicity, and emphasize the crucial need for integrated mitigation strategies that span agricultural management, technological innovation, and robust regulatory policy to address this pervasive public health challenge.

INTRODUCTION

From the frozen Arctic to the fields that feed us, per- and polyfluoroalkyl substances (PFAS) silently invade ecosystems worldwide. These persistent 'forever chemicals,' linked to serious toxicity, are stealthily entering our bodies through contaminated crops, demanding urgent answers about their hidden toll on human health, starting in our gut. PFAS comprise over 4,000 human-made compounds, are extremely persistent in the environment, and are found globally (Sunderland et al., 2018). Crops grown in contaminated soil readily absorb PFAS, introducing them into the human food chain (Gredelj et al., 2020). Since the gut is the primary site of initial exposure, this leads directly to our key question: How does

dietary exposure to PFAS from contaminated crops damage the human digestive system and contribute to systemic health problems?

This question is critically important for three reasons. First, PFAS exposure is nearly universal. Their ubiquitous presence is demonstrated by their detection in even the most remote and pristine environments far from direct industrial or urban sources. A 2024 study analyzing Arctic glacial runoff provides a stark example, finding significant concentrations of PFAS, including PFOA and PFOS, in regions assumed to be largely untouched by pollution (Lohmann et al., 2024). This underscores the role of long-range atmospheric and oceanic transport in the global dissemination of these compounds, indicating that contamination is not a local issue, but rather a planetary one. Second, their extreme persistence means they break down very slowly, taking years for their levels in blood to decrease significantly (Sunderland et al., 2018). Third, consuming contaminated food, especially homegrown crops, is a significant pathway for human exposure, though this route requires more targeted research (Gredelj et al., 2020).

This review synthesizes current knowledge to construct a cohesive narrative linking PFAS infiltration of the agricultural food chain to detrimental health outcomes, with a specific focus on the gastrointestinal tract as the critical gateway. We will first delineate the pathways by which PFAS contaminate soil and are taken up by crops. Then, we will examine how this initial gut damage can lead to systemic effects. However, constructing this narrative is hindered by critical knowledge gaps that impede a comprehensive understanding of the risks: existing research lacks long-term studies on chronic exposure and reflects a pronounced geographic and demographic bias. This review will therefore synthesize available evidence and highlight these gaps to guide future research priorities.

1.1 Definition and Historical Context

PFAS constitute a large class of synthetic chemicals, first developed in the 1940s and valued for their unique surfactant and stability properties (Buck et al., 2011). Their molecular structure, characterized by one of the strongest bonds in organic chemistry (carbon-fluorine), confers incredible resistance to water, oil, and heat. This led to their widespread incorporation into a vast array of industrial applications and consumer products, including non-stick cookware, water-repellent fabrics, firefighting foams, and food packaging materials.

The utility of PFAS, however, is unfortunately linked to their environmental persistence. The strength of the carbon-fluorine bond means these compounds are highly resistant to natural degradation processes such as hydrolysis, photolysis, and microbial breakdown (Kurwadkar et al., 2021). This recalcitrance means that PFAS released into the environment decades ago remain here today, earning them the colloquial moniker "forever chemicals."

1.2 Bioaccumulation and the Focus on PFOS and PFOA

The environmental persistence of PFAS is a primary driver of their global contamination. Once released, they accumulate in soils, sediments, and water bodies, where they can remain for decades, serving as a

long-term source of exposure (Kurwadkar et al., 2021). This persistence is compounded by their ability to bioaccumulate in living organisms and biomagnify up food chains. In humans, certain long-chain PFAS, such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), have been found to exhibit serum half-lives ranging from several years to over a decade, leading to sustained internal exposure even after external sources are removed (Fenton et al., 2021).

The scientific literature on PFAS bioaccumulation is vast, but it is not distributed evenly across the thousands of known compounds. Research efforts have historically focused on a limited number of legacy PFAS, primarily PFOS and PFOA, due to their widespread historical use, environmental prevalence, and early links to adverse health outcomes. Figure 1 highlights how the majority of the published research has concentrated on PFOS and PFOA, underscoring their roles as the most scrutinized legacy compounds.

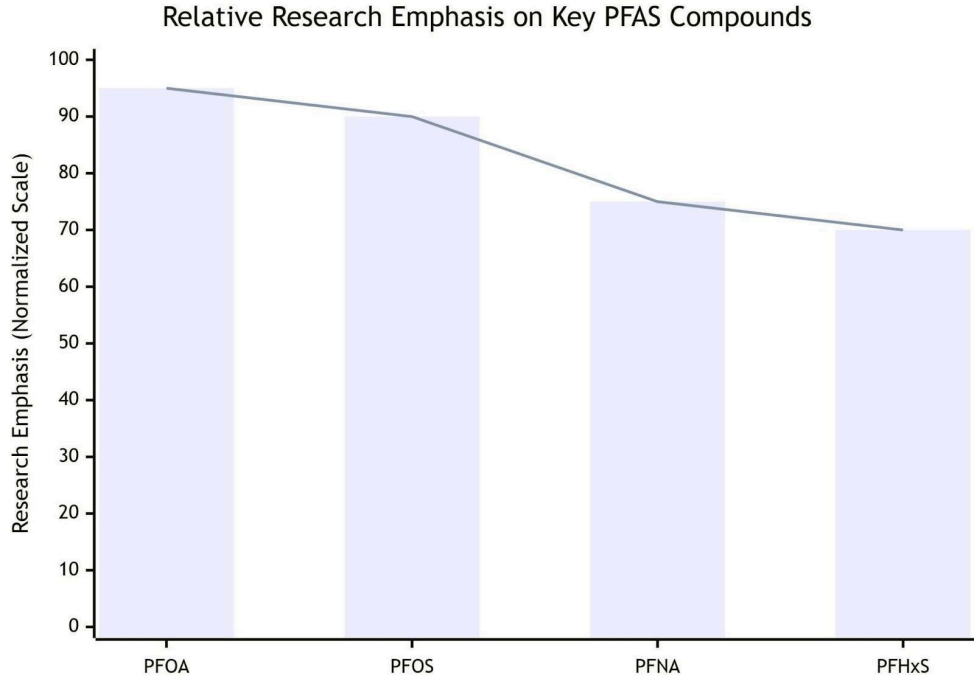

Figure 1. A bar chart ranking the most studied PFAS compounds (e.g., PFOS, PFOA)

Perfluorononanoic Acid (PFNA) and Perfluorohexane Sulfonic Acid (PFHxS) by the number of published scientific studies. PFOS and PFOA are consistently identified as the most prevalent and widely studied legacy PFAS. They are highlighted for their historical use, environmental contamination, and strong links to adverse health outcomes, making them a primary focus of regulatory action and scientific research (Garg et al., 2020; Ismail et al., 2023). PFNA and PFHxS are recognized as important replacement compounds for PFOA and PFOS that are increasingly detected in environmental and human samples. Their presence in electronic waste (Garg et al., 2020) and their detailed listing in chemical property tables (Ismail et al., 2023) underscore their growing significance in the PFAS research landscape. An effort was

made to prioritize two review articles to identify a consensus on the most frequently studied PFAS compounds based on their environmental prevalence and health impacts (Garg et al., 2020; Ismail et al., 2023). A third contextual study supported the finding that research is concentrated on a small subset of PFAS (Medina et al., 2025). The chart's rankings were derived from this consensus. This approach ensured reliability by synthesizing expert conclusions from within the peer-reviewed literature.

1.3 Toxicological Profile

The same stability that makes PFAS industrially useful also causes their toxicity. The extensive body of research on PFOS and PFOA has established strong associations with a range of adverse health effects. Epidemiological and toxicological studies have linked exposure to serious outcomes, including immunosuppression, endocrine disruption, and certain types of cancer, such as kidney and testicular cancer (Fenton et al., 2021; DeWitt et al., 2020; Fenton et al.,2020). The potential for these toxic mechanisms to impact human health can occur through exposure pathways, the most significant of which for the general population is the agricultural food chain. The U.S. Agency for Toxic Substances and Disease Registry (ATSDR, 2021) has set Minimal Risk Levels (MRLs) as low as 2 ng PFOS per kg of body weight per day and 3 ng PFOA per kg/day for chronic exposure, based on their devastating effects on the immune system and developmental toxicity (ATSDR, 2021). To contextualize, a child could exceed this daily threshold by consuming a single serving of leafy greens grown in moderately contaminated soil. This direct link between environmental contamination and human ingestion underscores the critical importance of understanding the specific mechanisms of gut-level toxicity, which serves as the gateway to the systemic health effects detailed in later sections.

2.0 ENVIRONMENTAL PATHWAYS TO HUMAN INGESTION

Understanding these pathways is critical for assessing human health risks and developing effective mitigation strategies. This section outlines the primary routes of exposure, focusing on the sources of soil contamination, the variables that influence crop uptake, and the resulting scale of dietary exposure.

2.1. Soil Contamination Sources: A Global Reservoir

Soil acts as a significant long-term sink and reservoir for PFAS, accumulating these persistent compounds from multiple anthropogenic sources and serving as a continuous source for contamination of groundwater and the food web (Brusseau et al., 2020; Ehsan et al., 2024). The primary sources include industrial discharge, the application of biosolids, and atmospheric deposition.

Industrial discharges from fluorochemical manufacturing plants represent a major point source. These facilities release PFAS into the air and water, which subsequently deposit onto or are used to irrigate

adjacent agricultural land. Empirical surveys in Europe show elevated soil PFAS concentrations up to ~10–20 km from many point sources, with manufacturing sites sometimes demonstrating a more extensive spread. For example, in one French industrial zone, soils within 0–10km showed up to ∑80 PFAS up to ~175 $\mu g \cdot kg^{-1}$, decreasing to ~0.1–46 $\mu g \cdot kg^{-1}$ at 10–20km and ~1.3–13.4 $\mu g \cdot kg^{-1}$ beyond 20km (Brusseau et al., 2020; Moghadasi et al., 2023; Saliu et al., 2025; Schroeder et al., 2021).

The impact of such point sources is starkly illustrated by a nationwide study of Chinese agricultural soils, which revealed that approximately 80-90% of the country's PFAS production facilities are concentrated in coastal regions, creating substantial regional disparities in contamination levels (Wang et al., 2024). This pattern is not isolated; similar industrial contamination hotspots have been documented across Europe and North America (Ehsan et al., 2024). Among all sources, the highest concentrations of PFAS in soil are consistently found at sites associated with aqueous film-forming foam (AFFF) usage (e.g., fire-training areas, military bases, and airports), where concentrations frequently exceed background levels by factors of 100 to 1,000 (Brusseau et al., 2020; Wang et al., 2024). PFAS plumes from AFFF-contaminated sites have been detected extending up to 3-5 kilometers from the source, highlighting their remarkable mobility through soil and groundwater. Similarly, PFAS manufacturing zones often exhibit soil concentration exceeding 10,000 ng/g, representing orders of magnitude higher levels than those detected in agricultural fields distant from industrial centers (Ehsan et al., 2024).

Biosolids application (the use of treated sewage sludge as fertilizer) represents a pervasive non-point pathway for introducing PFAS into agricultural systems. Wastewater treatment processes concentrate PFAS from industrial effluent, household products, and landfill leachate into the solid fraction, which is then applied to farmland as a nutrient-rich amendment. This practice leads to widespread, diffuse contamination, with detection frequencies exceeding 50% for multiple PFAS compounds in farmland soils that receive biosolids (Wang et al., 2024; Ehsan et al., 2024). The extreme persistence and bioaccumulative nature of PFAS mean that even minuscule daily intake leads to continuous buildup in the body over a lifetime. Therefore, the high detection rate in soil is a direct warning sign of a primary vector for chronic, low-dose exposure, silently introducing these harmful chemicals into the food web.

Finally, atmospheric deposition serves as a significant diffuse source, facilitating the long-range transport and global distribution of PFAS. Volatile PFAS precursors are released from industrial sites or product use areas and then evaporate. Once in the air, these chemicals travel, often reaching long distances. Then, they experience atmospheric transformation, a chemical process by which the volatile PFAS undergo oxidation and are converted into stable perfluoroalkyl acids (PFAAs). The stable acids are then deposited onto agricultural lands through precipitation. This process, known as global distillation or the “grasshopper effect,” explains how PFAS are detected in polar or high-altitude regions: these volatile compounds evaporate from warmer areas and undergo repeated cycles of deposition and re-emission as they travel, ultimately condensing and accumulating in remote regions (Brusseau et al., 2020; Evich et al., 2022; Sunderland et al.,2018; Wang et al., 2024).

2.2. Crop Uptake

The transfer of PFAS from contaminated soils into crops represents a critical pathway for human dietary exposure. PFAS are taken up by plants primarily through the root system via soil pore water and irrigation water, after which they can translocate into edible tissues such as leaves, fruits, and grains (Ehsan et al., 2024; Xu et al., 2022). This soil-to-plant transfer is chemically driven, plant-specific, and highly variable across agricultural systems. The differences between uptake and accumulation by crop type and PFAS compound are evident in Table 1.

A key driver of this variability is the compound's structure, particularly its chain length and functional group, which fundamentally influence both mobility and bioaccumulation factors (BAFS). A BAF is a tattoo that measures a plant's ability to concentrate a chemical from soil into its tissues, calculated as [PFAS in plant] / [PFAS in soil]. A BAF of 1 suggests equal concentration in the plant and the soil; a BAF of 10 (as seen with PFOA in lettuce) means the plant has ten times the concentration of the soil, and a BAF of 0.1 for grains means the concentration is one-tenth that of the soil. This value is directly proportional to the dietary risk; a higher BAF means a much greater amount of chemical is transferred into the food we eat from the same level of soil contamination. Compound structural differences directly shape the PFAS profiles found in food crops and ultimately, the human diet (Wang et al., 2024; Xu et al., 2022).

Short-chain PFAS (C4-C7) exhibit high water solubility, allowing greater mobility in soil-water systems and more effective root uptake. Once absorbed, these compounds readily translocate to shoots and leaves, often resulting in higher BAFs in aerial plant parts (Xu et al., 2022). In contrast, long-chain PFAS ($C \geq 7$ for PFCAs; $C \geq 6$ for PFSAs) tend to sorb more strongly to soil particles and plant root tissues, limiting their upward movement but still enabling notable accumulation, particularly in root vegetables or crops with high lip or protein content (Xu et al., 2022).

Crop Type	PFAS Compound	Observed Trend/Concentration

Root Vegetables (e.g., Carrot)	Long-chain PFAS (e.g., PFOA)	Demonstrates a strong propensity to accumulate long-chain PFAS compounds due to direct and prolonged contact with contaminated soil. These compounds are primarily stored within the peel (periderm) but can also translocate to the inner root core (parenchyma), making peeling only partially effective as a mitigation strategy. BAFs for root vegetables are consistently high, often comparable to or exceeding those of leafy greens for long-chain compounds, thus making them a high-risk crop category.

Cereals/Grains (e.g., Wheat, Maize)	Various PFAS	Uptake and translocation follow a distinct pattern: Root > Straw > Grain. While roots absorb PFAS from soil, the compounds have limited mobility to the aerial parts of the plant. The vascular system acts as a barrier, resulting in significantly lower accumulation in the edible grain (seed) compared to vegetative tissues. BAFs for grains are typically very low (often <0.1), indicating that the grain contains a fraction of the soil concentration, posing a lower direct dietary risk from the grain itself.

Gourd Vegetables (e.g., Zucchini)	PFBA, PFOA	Show a notable ability to uptake both short-chain (e.g., PFBA) and legacy long-chain (e.g., PFOA) compounds. Short-chain PFAS, being more water-soluble, are more readily transported through the xylem and can accumulate in the watery, fleshy fruit. The distribution can be uneven, often with higher concentrations in the peel than in the pulp. BAFs can be moderate but are highly variable depending on the specific compound's chain length and functional group.

Table 1: PFAS accumulation in different crops. General trends based on BAF (Bioaccumulation Factor) by plants; all information comes from Xu et al. (2022).

Long-chain PFAS like PFOA and PFOS often remain dominant in soils, are highly persistent, and can still be major contributors to dietary intake due to their potent ability to bioaccumulate in humans and their prevalence. Therefore, the ultimate risk from any contaminated field is a product of both the concentration and diversity of PFAS in the soil and their respective BAFs for the crops grown there. This interplay between pervasive soil contamination and compound-specific uptake mechanics is what makes PFAS such a complex and persistent challenge to food safety.

3.0 HUMAN EXPOSURE AND HEALTH EFFECTS

3.1 Multi-Source Exposure Context

PFAS exposure occurs through a complex web of pathways, encompassing both dietary and non-dietary sources. Exposure can occur via indoor dust, cleaning supplies, consumer products, and occupational settings (e.g., firefighting, PFAS manufacturing) (Sunderland et al., 2018; Espartero et al., 2022). Dietary intake, however, is consistently identified as a dominant and particularly insidious pathway for chronic, low-level exposure in the general population (Sunderland et al., 2018). This is especially true for populations consuming contaminated crops, seafood, and animal products derived from PFAS-impacted areas (Sunderland et al., 2018; Chukwuonye et al., 2024).

A major and increasingly recognized contributor within the dietary pathway is PFAS migration from food-contact materials. Paper- and board-based items designed for greasy or hot foods, such as fast-food wrappers, french-fry boxes, pizza boxes, microwave popcorn bags, and molded "compostable" fiber containers, frequently contain extractable PFAS that can transfer into food during use. Targeted surveys report PFAS in 40-90% of tested packaging materials, with total fluorine or individual PFAS levels typically ranging from tens to several hundred ng/g (Dueñas-Mas et al., 2023; Lerch et al., 2023; Loureiro et al., 2024; Zabaleta et al., 2020). Microwave popcorn bags and grease-resistant wrappers often exhibit the highest values, exceeding 1000 ng/g, while pizza boxes and general cardboard containers generally fall below 100 ng/g, depending on coating chemistry and supply-chain practices. Migration increases with heat, grease content, and contact time, and molded or recycled fiber products may retain background PFAS even when not intentionally treated.

Regulatory differences influence these concentrations: the European Union has moved towards a comprehensive ban on PFAS in food packaging, while the United States relies primarily on voluntary phase-outs and state-level restrictions (Loureiro et al., 2024). These policy contrasts complicate direct cross-regional comparisons but highlight meaningful divergence in exposure potential.

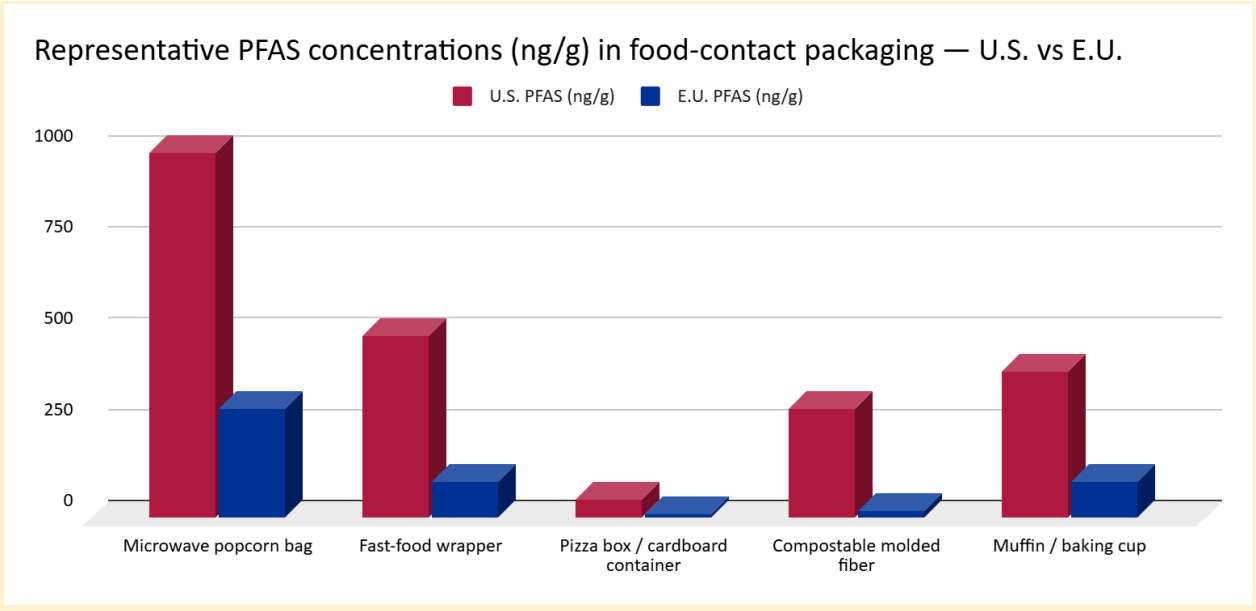

Figure 4 displays a comparative bar chart of estimated PFAS concentration in common food-contact packaging items across the U.S. and E.U. markets. Items such as microwave popcorn bags, grease-resistant wrappers, molded-fiber "compostable" containers, pizza boxes, and backing-cup liners were selected because of their known susceptibility to PFAS treatment. The U.S. values show markedly higher representative concentration (e.g., ~1000 ng/g in popcorn bags), reflecting slower phase-outs and continued use of legacy fluorinated coatings. In contrast, E.U. concentrations are substantially lower (e.g., ~300 ng/g for similar items), consistent with earlier adoption of bands and stricter regulatory oversight. This disparity underscores a critical point: exposure risk is driven not only by the presence of PFAS but by the magnitude of residual chemical burden in materials that directly contact food (Dueñas-Mas et al., 2023; Lerch et al., 2023; Loureiro et al., 2024).

Together, these observations demonstrate that PFAS dietary exposure stems from both environmental contamination and packaging-mediated transfer. This multi-source exposure context underscores the importance of the gastrointestinal tract as the body's primary site of initial PFAS contact and associated toxicity (Espartero et al., 2022).

3.2 Comparative Vulnerability in Rural and Urban Populations

Dietary PFAS exposure is shaped by community-level food sources, water quality, and environmental contamination patterns. These exposure pathways differ substantially between rural and urban populations.

Rural Vulnerability: Rural communities located near major contamination sources such as chemical manufacturing sites, agricultural areas amended with biosolids, and military bases where aqueous

film-forming foams (AFFF) were used, face disproportionately high PFAS exposure (Chukwuonye et al., 2024; Sunderland et al., 2018). Irrigation with contaminated water represents a particularly important vector in these regions (Ehsan et al., 2024). Since many rural households rely on locally grown produce, livestock raised on contaminated pasture, and groundwater for drinking, contamination in the environment transfers directly into their diet. These conditions have been associated with significantly elevated serum PFAS levels in rural populations compared to national averages (Chukwuonye et al., 2024). Figure 2 illustrates this heightened risk by modeling the relative contribution of local food and water pathways to overall PFAs intake.

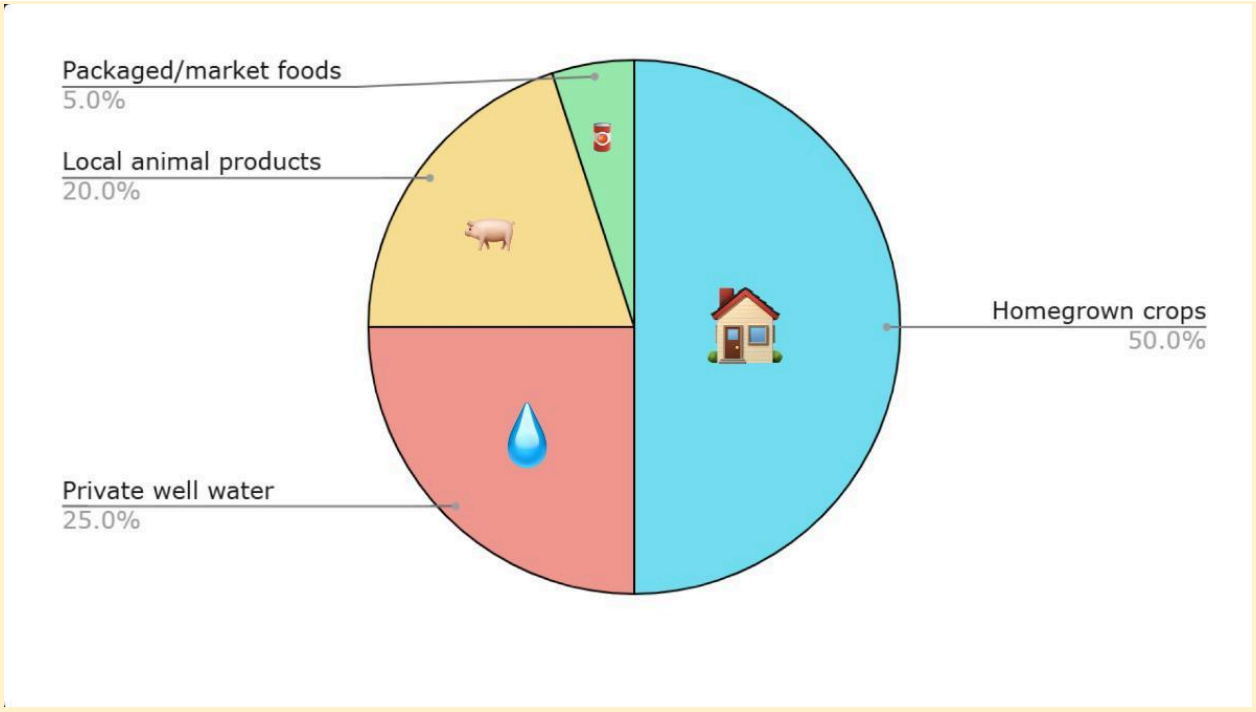

Figure 2. Estimated dietary PFAS intake for populations in rural areas, highlighting contributions from homegrown crops, private well water, and local animal products. Two major review articles served as the foundational references for identifying which PFAS compounds are most frequently studied due to their environmental prevalence and health impacts (Garg et al., 2020; Ehsan et al., 2024). A third contextual study supported the finding that research is concentrated on a small subset of PFAS (Medina et al., 2025).

Urban Vulnerability: Urban populations experience a more diffuse but still meaningful set of dietary PFAS exposures. The mix of exposure is depicted in Figure 3 below. Most food is obtained through commercial supply chains, which may include items produced in contaminated agricultural regions or packed using PFAS-treated materials (Sunderland et al., 2018). Although urban residents are less dependent on local environmental conditions than rural populations, home gardening can still create a direct exposure route, particularly when soil receives atmospheric PFAs deposition or when municipal

compost containing biosides is used (Sunderland et al., 2018). As a result, urban exposures reflect a complex mix of packaged-food intake and potential localized soil-to-plant transfer, creating a multifaceted but less well-characterized risk profile.

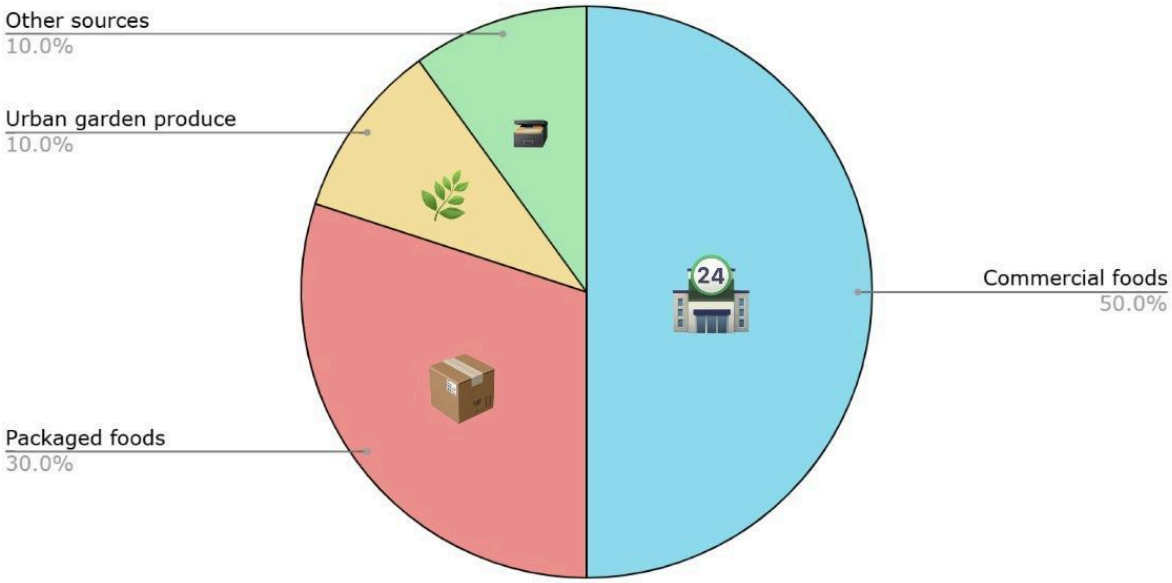

Figure 3. Estimated dietary per- and polyfluoroalkyl substances (PFAS) intake pathways for an urban population, highlighting dominant sources including commercially produced food, packaged foods, and produce from urban gardens. Figure 2. Estimated relative contribution of different dietary pathways to PFAS intake in a hypothetical rural population.

3.3 Mechanisms of Toxicity: From Gut Disruption to Systemic Disease

The digestive system serves as the first line of defense against dietary PFAS, making it a primary target for their toxic effects. The mechanisms are multifaceted, involving direct damage to the intestinal barrier and indirect effects mediated through the gut microbiome. This initial damage acts as a gateway to the systemic health burdens associated with PFAS.

3.3.2 Direct Gut Toxicity: Barrier Disruption and Impaired Digestion

PFAS are surfactants, a property that allows them to disrupt the structural integrity of the intestinal epithelial lining. The disruption of tight junctions between epithelial cells increases intestinal permeability, or "leaky gut" (Espartero et al., 2022). This condition enables the translocation of PFAS,

bacterial endotoxins (e.g., LPS), and other pro-inflammatory molecules from the gut lumen into the systemic circulation, potentially initiating widespread inflammatory responses (Espartero et al., 2022; Fenton et al., 2020). Furthermore, PFAS can interfere with bile acid metabolism and function, impairing lipid digestion and absorption and potentially contributing to malabsorption issues and metabolic dysregulation (Fenton et al., 2020).

3.3.3 Indirect Gut Toxicity: Microbiome Dysbiosis

The human gut microbiome is highly sensitive to environmental pollutants like PFAS, exposure to which is linked to dysbiosis, a state of microbial imbalance characterized by a reduction in beneficial bacteria and an increase in pathogenic ones (Espartero et al., 2022). A key consequence of this shift is the impaired production of essential short-chain fatty acids (SCFAs), such as butyrate, which are critical for colonocyte health, T-cell development and immune regulation, and the maintenance of intestinal barrier integrity. (Fenton et al., 2020; Espartero et al., 2022; Kim, 2023; Liu et al., 2023). This microbial imbalance, coupled with the direct irritant effects of PFAS, triggers a state of chronic low-grade inflammation within the gastrointestinal tract. This persistent inflammation activates the gut-associated lymphoid tissue (GALT), a specialized mucosal immune system comprising Peyer's patches, isolated lymphoid follicles, and mesenteric lymph nodes that constantly monitor intestinal antigens (Mörbe et al., 2021; Mowat et al., 2014).

The chronic activation of GALT is a critical and detrimental outcome. While acute GALT activation is a protective immune response, its chronic stimulation disrupts immune homeostasis. This leads to an exaggerated pro-inflammatory cytokine production (e.g., TNF-α, IL-6). These cytokines act in a feedforward loop: TNF-α induces IL-6 production via NF-κB, JAK/STAT3, and MAPK signalling, while IL-6 further sustains these pathways, though its receptor /gp130 complex, collectively amplifying inflammation, impairing regulatory feedback, and promoting mucosal tissue injury (Kang et al., 2019; Tanabe et al., 2010). They can result in a loss of oral tolerance, which is the immune system's ability to recognize harmless substances in food and gut microbes and avoid mounting an unnecessary immune response against them. Disruption of this tolerance can contribute to food allergies and hypersensitivity reactions (Mörbe et al., 2021; Mowat et al., 2014; Wambre et al., 2018).

Consequently, this self-perpetuating cycle of inflammation can damage mucosal structures and increase susceptibility to conditions like inflammatory bowel disease (IBD) (Mowat et al., 2014). Furthermore, a dysregulated GALT response is associated with compromised immune function, including altered T-cell populations, which may elevate the risk of systemic immune dysregulation and septic complications (Mörbe et al., 2021; Mauser et al., 2021). Therefore, PFAS-induced chronic GALT activation represents a harmful shift from protective immune surveillance to pathological inflammation, significantly exacerbating gut toxicity and broader systemic health risks.

3.4 Systemic Health Effects: The Gut-System Axis

Gut-based harm is not limited to the gut. Chronic, systemic inflammation is heightened by the combined impact of microbiome dysbiosis and a compromised gut barrier. This gut-system axis offers a compelling explanation for how exposure to dietary PFAS may contribute to the emergence of a number of chronic illnesses. Epidemiological studies have also associated elevated serum PFAS levels with a significantly increased risk of kidney and testicular cancer, thyroid disease, ulcerative colitis, and elevated cholesterol (Fenton et al., 2020; EBioMedicine, 2023).

Hepatic and Renal Damage: The liver and kidneys are major sites of PFAS accumulation and elimination. Systemic inflammation and the oxidative stress caused by PFAS can lead to liver steatosis (fatty liver disease), hepatocellular damage, and altered liver enzyme function, such as elevated ALT (Alanine Aminotransferase) and AST (Aspartate Aminotransferase) levels (Fenton et al., 2020; Espartero et al., 2022). Similarly, the kidneys, which are responsible for filtering blood, are vulnerable to PFAS-induced toxicity. This may impair glomerular filtration rate and contribute to renal dysfunction (Espartero et al., 2022).

Endocrine Disruption: PFAS are well-established endocrine disruptors. Their structural similarity to fatty acids allows them to interact with nuclear receptors such as the peroxisome proliferator-activated receptors (PPARs), which play a central role in lipid and glucose metabolism. Mechanistically, PFAS molecules exploit their amphiphilic nature, bearing a hydrophobic fluorinated tail and a charged or polar head group to engage with biological systems: the hydrophobic fluorinated tail partitions into non-polar pockets (e.g., receptor ligand-binding domains or lipid membranes), while the polar/charged head interacts electrostatically with positively charged residues or domains. This combination of hydrophobic and electrostatic interactions underlines how PFAS can bind to and activate PPARs. One study explained, "PFOA activates PPARγ through binding to the PPARγ ligand binding domain (PPARγ LBD), leading to increased expression of PPARγ-controlled target genes" (Pedric et al., 2024). Once PPAR signalling is perturbed, metabolic regulation is disrupted, leading to thyroid dysfunction (e.g., reduced T3/T4 hormones), reproductive issues, and an increased risk of metabolic disorders (EBioMedicine, 2023; Espartero et al., 2022; Fenton et al., 2020; Lei et al., 2023).

Immunosuppression: While PFAS overstimulate certain aspects of the immune system, such as the chronic activation of gut-associated lymphoid tissue and the production of pro-inflammatory cytokines, they simultaneously suppress other components, including antibody-mediated responses and overall immune competence (Fenton et al., 2020; EBioMedicine, 2023). PFAS interfere with adaptive immunity by disrupting B-cell and T-cell development and function, impairing antigen-specific antibody generation and weakening immune memory (Crawford et al., 2023; Zhang et al., 2022). Mechanistically, PFAS can alter cell signaling pathways regulated by nuclear receptors (e.g., PPARs and NF-κB) and disrupt the integrity of immune cell membranes, hindering lymphocyte activation and antibody synthesis (Feton et al., 2020).

This impaired immune signaling is evidenced by reduced antibody responses to vaccines (e.g., tetanus, diphtheria), decreased resistance to infections, and potentially increased susceptibility to allergies and

autoimmune disease. Gut-driver inflammation likely amplifies these immune deficits (Feton et al., 2020; EBioMedicine, 2023).

Metabolic Dysfunction: Through the gut-liver axis, PFAS-induced dysbiosis and inflammation are increasingly linked to metabolic syndromes, including obesity, insulin resistance, and dyslipidemia. The disruption of PPAR signaling and other metabolic pathways can lead to elevated cholesterol levels and an increased risk of developing type 2 diabetes (EBioMedicine, 2023; Espartero et al., 2022; Fenton et al., 2020).

3.5 Summary of Health Mechanisms

The journey of PFAS from contaminated soil to the human gut represents a critical pathway for population-wide exposure. The digestive system is not merely a passive conduit but an active site of PFAS-induced toxicity, where barrier function is compromised and inflammation is initiated (Espartero et al., 2022; Fenton et al., 2020). This gut-level damage acts as a gateway, contributing to the systemic health burdens associated with PFAS, including metabolic, immune, endocrine, and hepatic diseases (EBioMedicine, 2023; Fenton et al., 2020; Sunderland et al., 2018). Addressing the unique vulnerabilities of both rural and urban populations, particularly through the protection of agricultural integrity and food safety, is paramount to mitigating the public health impact of these persistent "forever chemicals" (Chukwuonye et al., 2024; Sunderland et al., 2018).

CONCLUSION

This review has synthesized evidence to construct a clear and concerning pathway: PFAS persist in agricultural soils through industrial discharge, biosolids application, and atmospheric deposition; they are readily taken up by food crops, particularly leafy and root vegetables; and upon consumption, they initiate toxic effects within the human digestive system. The gut, as the primary site of exposure, suffers direct barrier disruption and microbiome dysbiosis, creating a state of chronic inflammation that serves as a gateway to systemic health problems, including immunosuppression, endocrine disruption, and metabolic dysfunction.

Dietary exposure represents a major pathway of PFAS entry into the human body, with implications that extend to both rural and urban populations. While point sources create heightened vulnerabilities for communities in proximity to contamination sites, the diffuse contamination of the global food supply highlights that dietary risk is a population-wide concern.

While this review synthesizes the current understanding of PFAS transmission from crops to human health, it is constrained by significant gaps in the existing literature. Current evidence is limited by a

pronounced geographic bias, with most data originating from the U.S. and E.U., leaving exposure and health outcomes in the Global South largely uncharacterized (Sunderland et al., 2018; Wang et al., 2024). Additionally, much of the research relies on hydroponic studies, which cannot replicate the complexity of real-world soil systems and crop–soil interactions (Xu et al., 2022). There is also a critical shortage of longitudinal studies evaluating the effects of chronic, low-dose dietary PFAS exposure on gut health and systemic outcomes (Espartero et al., 2022; Fenton et al., 2020). Isolating dietary PFAS exposure from other routes (e.g., drinking water, packaging, dust) remains methodologically challenging (Sunderland et al., 2018). Finally, the toxicological profiles of PFAS mixtures remain poorly understood, as most studies focus on individual compounds rather than real-world exposure scenarios (DeWitt et al., 2020; EBioMedicine, 2023).

A comprehensive strategy integrating scientific research, evidence-based policy, and agricultural best practices will be necessary to mitigate the long-term health and ecological consequences of PFAS. Therefore, moving forward, effective mitigation requires a concerted effort across several fronts:

1. **Mitigation strategies:** Effective mitigation of PFAS contamination in the agricultural food chain requires a multitiered approach that integrates technological, agronomic, and policy-driven interventions. Since PFAS are highly stable and resistant to conventional degradation pathways, complete elimination from environmental systems remains unfeasible. Accordingly, mitigation efforts must prioritize reducing environmental release, immobilizing contaminants in soil, limiting plant uptake, and advancing destruction technologies.

2. **Technological Innovation:** Promising remediation strategies are emerging, from soil washing and the application of PFAS-degrading microbes to the use of soil amendments like biochar to sequester contaminants and reduce crop uptake.

3. **Agricultural Management:** Shifting cultivation towards low-uptake crops (e.g., grains over leafy greens) in contaminated areas and revising the use of biosolids are critical interim steps to reduce exposure.

4. **Robust Policy and Informed Consumer Action:** Regulatory momentum, such as the U.S. EPA's PFAS Strategic Roadmap, must be accelerated and globalized. This includes supporting bans on contaminated biosolids and funding the development of safer alternatives. Concurrently,

increasing public awareness and disseminating best practices for home gardening may reduce exposure at the community level.

5. **Research:** Addressing PFAS contamination will require closing the critical knowledge gaps identified in this review, including the need for longitudinal dietary exposure studies, mixture toxicology, and expanded global monitoring.

The journey of per- and polyfluoroalkyl substances (PFAS) from industrial application to global contaminants and into the human body is a salient example of the intersection between modern environmental contamination and public health challenges. As the world confronts the legacy of PFAS, the challenge ahead lies in coupling scientific clarity with decisive action, transforming what we now understand into meaningful protection for both the ecosystem and human health.

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